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# Mitochondrial biogenesis in adipose tissue: can exercise make fat cells 'fit'?

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White adipose tissue (WAT) is now considered an active endocrine organ and its dysregulation predicts metabolic diseases. Much emphasis has recently been placed on the role of mitochondrial biogenesis in adipose tissue, since diabetic rodents, as well as overweight or obese humans with insulin resistance (IR), have reduced WAT mitochondrial content and function. Treatments that increase mitochondrial biogenesis in WAT could potentially improve IR and reduce obesity, making them a hot pursuit. Some pharmacological treatments including peroxisome proliferator-activated receptor $\gamma$ (PPAR$\gamma$) agonists (e.g. thiazolidinediones, TZDs) show promise in this area, but carry with them unfavourable side effects including weight gain, making behavioural interventions to improve WAT metabolic function an attractive alternative. Exercise training is known to increase mitochondrial biogenesis in skeletal muscle, but surprisingly little is known about the effect of exercise on mitochondrial biogenesis in WAT. In a recent article in *The Journal of Physiology*, Sutherland and colleagues examined the effect of both acute and chronic exercise on markers of mitochondrial biogenesis in WAT (Sutherland *et al.* 2009) and explored potential mechanisms by which exercise might exert these effects.

Sutherland *et al.* exercise-trained male Wistar rats using swimming exercise (2 h day$^{-1}$, 7 days week$^{-1}$ for 4 weeks). To assess mitochondrial protein content, the respiratory chain complex proteins COXIV (cytochrome *c* oxidase subunit IV) and CORE1 (cytochrome *c* oxidoreductase core I subunit) were analysed. In addition, gene expression levels of PPAR$\gamma$ coactivator-1 (PCG-1$\alpha$, a major regulator of mitochondrial biogenesis), and mitochondrial transcription factor A (Tfam, a transcription factor involved in mitochondrial biogenesis downstream of PGC-1$\alpha$) were measured in WAT. Citrate synthase activity was measured to confirm that the increases in protein content and gene expression corresponded with increases in mitochondrial function.

## Exercise training increases mitochondrial content and function

The training regimen produced predictable changes in body composition such that trained rats gained less weight and had smaller fat pads than did sedentary rats. More importantly, Sutherland and colleagues demonstrated, for the first time in WAT, that exercise training increases PGC-1$\alpha$ (but not PGC-1$\beta$) and Tfam mRNA expression, as well as COXIV and CORE1. Citrate synthase activity in the WAT of the healthy non-obese rats was also elevated in trained versus untrained animals. These changes were consistent in both epididymal and retroperitoneal fat pads, two separate visceral WAT depots. The authors proceeded to evaluate potential mechanisms governing these exercise-induced changes in WAT mitochondrial gene expression.

## Acute exercise increases PGC-1$\alpha$, but not Tfam

In addition to assessing the effects of exercise training on mitochondrial content and function, changes were assessed following an acute exercise bout. In this experiment, the 2 h bout of exercise increased gene expression of PGC-1$\alpha$ (but not Tfam) in both fat depots, which returned to control levels by 4 h post-exercise. The transient nature of the PCG-1$\alpha$ up-regulation after the acute exercise bout suggests that exercise training is necessary for increased mitochondrial biogenesis and that the training effects observed were not explained by the residual effect of the last training bout.

## Adrenaline: a potential mechanism?

Adrenaline (a catecholamine released into the circulation with sympathetic stimulation such as exercise) has been shown to induce PCG-1$\alpha$ in tissues such as brown adipose tissue, skeletal muscle and liver, but its effects on WAT are not known. The authors employed WAT organ culture to assess the effects of adrenaline on mitochondrial biogenesis, revealing a dose-dependent relationship between adrenaline and PGC-1$\alpha$. During a time course experiment using the lowest dose of adrenaline (1 $\mu$M), PGC-1$\alpha$ peaked following a 2 h exposure, and returned to near control levels by 12 h. The time course in culture resembled that of acute exercise, with PGC-1$\alpha$ expression maximized early on and falling thereafter. Tfam expression did not peak until 12 h of exposure. This delayed induction of Tfam gene expression may account for the lack of effect following acute exercise, which may have been augmented 6 or 12 h post-exercise.

Following the WAT culture data, an *in vivo* experiment was performed to determine if the exercise effect could be prevented by blocking adrenaline. Administration of a $\beta$-blocker (propranolol) prior to exercise attenuated the exercise-induced rise in PGC-1$\alpha$ by ~40%, suggesting that at least part of the mechanism by which exercise increases mitochondrial biogenesis in WAT involves an increase in circulating adrenaline.

## Interpretation and implications

This paper by Sutherland *et al.* documents their important discovery that, even in the absence of mitochondrial dysfunction, exercise is sufficient in initiating beneficial changes in WAT. What remains unclear is the extent to which these results can be translated to populations that are affected by reduced mitochondrial function, such as obese, diabetic, or aged individuals. PPAR-$\gamma$ agonists (TZDs) have been demonstrated to induce mitochondrial biogenesis in WAT of insulin resistant mice (Rong *et al.* 2007). What is not known is whether exercise is a powerful enough treatment to compete with such pharmacological therapies.

While researchers frequently compare visceral to subcutaneous WAT, Sutherland *et al.* focused their study on two visceral WAT depots which are both more metabolic when compared to subcutaneous WAT. Moreover, excess visceral WAT is an independent risk factor for metabolic


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syndrome and other complications. Their findings suggest that metabolic differences may exist even among visceral depots. In epididymal WAT acute exercise-induced stimulation of PGC-1$\alpha$ mRNA expression is blunted compared to the retroperitoneal depot, at least acutely. Paradoxically, this depot is much more responsive to $\beta$-adrenergic stimulation *in vivo*. The explanation behind these contrasting findings is not clear. Furthermore, no difference between depots was apparent in changes in protein content or citrate synthase activity following chronic exercise training.

The fact that the exercise effect was not completely abolished upon administration of the $\beta$-blocker raises questions about the mechanism(s) responsible for the remaining ~60% of the exercise effect. The authors postulate a few potential mechanisms behind their observed effects, including exercise-mediated increases in interleukin-6 and/or thyroid hormone. Inflammation and IR in WAT are known to down-regulate mitochondrial biogenesis. Exercise training reduces IR and attenuates WAT inflammation (Vieira *et al.* 2009), providing other potential mechanisms. However, Sutherland and colleagues previously demonstrated disconnect between WAT mitochondrial protein and IR (Sutherland *et al.* 2008). Perhaps the results seen in the present study were secondary to other exercise training-induced metabolic adaptations.

Further research is necessary to elucidate the mechanisms leading to chronic exercise adaptations. Importantly, PGC-1$\alpha$ is not the only regulator of mitochondrial biogenesis. The authors mention that ciliary neurotrophic factor (CNTF, a growth factor with potential anti-obesity properties) has also been demonstrated to induce WAT mitochondrial biogenesis (Crowe *et al.* 2008). Additionally, metabolic changes such as up-regulation of WAT GLUT-4 or enhanced metabolic flux may contribute to mitochondrial regulation. The fact that exercise training increases WAT GLUT-4 expression (Stallknecht *et al.* 1993) supports this contention. Intriguingly, PGC-1$\alpha$, in muscle, has been shown to up-regulate proteins involved in fuel transport, such as GLUT-4 and AMPK (Benton *et al.* 2008) as well. These plausible links between exercise and enhanced mitochondrial biogenesis warrant further investigation.

There is controversy in the literature regarding the best model of exercise for animal studies. Swim training has been criticized for its stressful nature. It is interesting that the authors chose swimming as their exercise model since the major mechanism that they were investigating was an increase in adrenaline, a response commonly associated with stress. However, the authors exposed all of the rats to the water in order to control for this 'stress effect'. Details about the training protocol, particularly session intensity, were not specified, but may be an important mediator of the acute and adaptive exercise effects. Moreover, the training duration in this study ($2\ \mathrm{h\ day^{-1}}$, $7\ \mathrm{days\ week^{-1}}$) may not be attainable by humans, raising questions about the translational aspects of this study.

Since the authors' rationale for using the $\beta$-blockade was to block circulating adrenaline, it would have been nice to see the levels of adrenaline in the circulation. Additionally, the use of propranolol, a non-selective $\beta$-blocker, may down-regulate PGC-1$\alpha$ gene expression even in control animals, which the authors did not report. Incorporating the opposite approach, testing the effect of injections of adrenaline (similar to circulating levels during exercise, ~15 nM) to sedentary animals on PGC-1$\alpha$ mRNA in comparison to exercise-trained animals would help to verify the causal role of adrenaline.

As WAT metabolic function is known to correlate strongly with whole body metabolic function, this study would have been strengthened if metabolic effects were assessed, such as IR and/or energy expenditure. Whether an exercise-mediated increase in mitochondrial biogenesis is sufficient to mitigate obesity and/or metabolic disturbances remains unknown and should be addressed in future studies.

In summary, exercise increases mitochondrial biogenesis in rat WAT and the mechanism may involve an exercise-mediated increase in adrenaline (Sutherland *et al.* 2009). This suggests that exercise may be a promising behavioural approach to enhance the 'fitness' of fat cells. These findings bring to the forefront yet another reason why exercise training is a vital behavioural approach for obesity reduction and improved metabolic health. Importantly, the amount and intensity of exercise necessary to cause such changes in fat in humans is yet to be determined, but is likely to soon become an actively pursued area of research.

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