

Fatty acid-induced mitochondrial uncoupling in adipocytes as a key protective factor against insulin resistance and beta cell dysfunction: do adipocytes consume sufficient amounts of oxygen to oxidise fatty acids?

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Abbreviation

HAART highly active anti-retroviral therapy

To the Editor: The phenotype of patients with various forms of congenital lipodystrophy has indicated that proper storage of triacylglycerol in peripheral adipocytes is essential to prevent formation of ectopic fat deposits and development of type 2 diabetes [1]. A similar situation with induced peripheral lipodystrophy and elevated risk for type 2 diabetes is seen in patients undergoing highly active anti-retroviral therapy (HAART). In these patients, there is a 30–50% decline in mitochondrial copy number as a result of HAART [2].

Based on these and other observations, we have recently put forward the hypothesis that one of the functions of mitochondria in adipose tissue is to prevent leakage of fatty acids into the circulation [3]. This mitochondrial activity attenuates the development of ectopic triacylglycerol deposits in the liver and other tissues that would otherwise contribute to the development of whole body insulin resistance and pancreatic beta cell damage. Mitochondria contribute to efficient confinement of fatty acids within adipocytes by oxidative removal of fatty acids, liberated from the triacylglycerol pool, by uncoupled beta oxidation. In addition, mitochondria may provide glyceroneogenic substrates, which contribute to re-esterification of fatty acids. As a net result, there are less fatty acids available to the circulation for redistribution to other compartments of the body [3]. A recent study provided supporting evidence for this concept by showing that the mitochondrial DNA copy number in human adipocytes is positively associated with lipogenesis in adipocytes [4].

Recently, Frayn et al. have argued against this biochemical mechanism [5]. They point out that fatty acid oxidation is not a major pathway in white adipocytes and that oxygen consumption by adipose tissue is insufficient to oxidise substantial amounts of fatty acids [6].

We fully agree with the point made by the authors that fatty acid oxidation by adipocytes is not a major pathway compared with muscle. However, we hold a different view on the quantitative interpretation of these data: in our model there is no need for a high rate of fatty acid oxidation in adipose tissue per time unit, as fatty acid redistribution from peripheral tissue to the liver is a slow process, taking several years. For instance, in individuals in whom mitochondrial copy number is acutely reduced as result of starting HAART, it takes 18–24 months before redistribution of body fat becomes clinically manifest [7].

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Therefore, the amount of fatty acids that undergoes redistribution per time unit is very small. Thus, mitochondria in adipocytes only need to remove a small amount of fatty acids per time unit to protect against redistribution of body fat. By using the oxygen consumption data of Frayn et al. and others [5, 6] or using similar data from other studies [8, 9], one can calculate that oxygen consumption by adipose tissue is sufficient to prevent redistribution of >1.5 kg of fat out of 10 kg of peripheral adipose tissue to the liver within a 3 year period, a realistic clinical situation.

Therefore, in our opinion, adipose tissue is able to oxidise substantial amounts of fatty acids over a long period by mitochondrial beta oxidation. This process may over time attenuate ectopic deposition of those fatty acids. Since mitochondria also contribute to formation of glycerol 3-phosphate, needed for re-esterification of fatty acids within adipocytes, mitochondria in adipocytes have the ability to protect the organism to a certain extent against leakage of fatty acids into the circulation and thus, redistribution of body fat. As Frayn et al. [5] have pointed out, brown adipose tissue is indeed more active in uncoupled oxidative disposal of fatty acids compared with white tissue. Recent evidence also suggests that brown adipose tissue is present in variable amounts and at multiple sites in humans, contrary to earlier reports [10]. This recently recognised situation further enhances the capacity of the adipose compartment to remove fatty acids through uncoupled beta oxidation.

In order to understand the mechanism by which mitochondria in adipocytes contribute to the control of body fat distribution during the development of the metabolic syndrome, additional studies are needed, comprising quantification of fatty acid fluxes in relation to re-esterification and oxidation in adipose tissue. These studies should include study of adipose tissue from individuals with normal glucose tolerance and from those with developing glucose intolerance.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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