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Adipose tissue mitochondrial function is modulated by antioxidants

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, den 15 oktober, klockan 9.00

av Eduard Peris Franquet

Fakultetsopponent:

Martin Jastroch, Universitetslektor vid Institutionen för molekylär biovetenskap Wenner-Grens institut

Stockholm Universitet, Sverige

Avhandlingen baseras på följande delarbeten

I. *Peris, E., Micallef, P., Paul, A., Palsdottir, V., Enejder, A., Bauzá-Thorbrügge, M., Olofsson, C. S., and Wernstedt Asterholm, I.* Anti-oxidant treatment induces reductive stress associated with mito-chondrial dysfunction in adipocytes. *J Biol Chem 294, 2340-2352 (2019).*

II. *Peris, E., Bauzá-Thorbrügge, M., Micallef, P., Bartesaghi, S., Ben-rick, A. and Wernstedt Asterholm, I.* Prolonged N-acetylcysteine treatment induces mitohormesis in adipose tissue. *Manuscript.*

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Adipose tissue mitochondrial function is modulated by antioxidants

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ABSTRACT

Antioxidants are widely used as reactive oxygen species (ROS) scavenging agents in experimental research and in conditions where oxidative stress plays a primary role. However, the effect of antioxidant supplementation on white and brown adipose tissue functionality is understudied, and the role of ROS and/or antioxidant treatment during adipose tissue browning, a process in which the adipocytes' mitochondrial density and activity increase, is largely unknown.

In **paper I**, by using antioxidants and ROS-sensitive fluorescent probes in cultured β3-AR-stimulated adipocytes, we observed that 24-48-hour antioxidant treatment increases the mitochondrial ROS production associated with reduced respiration and increased glycolysis. Moreover, treatment of mice with the antioxidant N-acetylcysteine (NAC) blunted the β3-AR agonist-induced browning response of white adipose tissue and reduced the mitochondrial activity in brown adipose tissue even in the absence of β3-AR stimulation. Previous studies have shown positive effects of prolonged NAC treatment on whole-body metabolism in mice. In light of these seemingly contradictory results, we hypothesize that chronic antioxidant exposure, in a dose-dependent manner, can lead to so-called mitohormesis. Indeed, in **paper II**, by treating mice with a set of different NAC doses across a defined time course, we found that prolonged supplementation with a high dose of NAC leads to increased mitochondrial function of white adipose tissue, reduced fat mass and improved insulin sensitivity. In summary, this thesis demonstrates that the adipose tissue response to antioxidant treatment in mice is biphasic and tightly connected to the adipose tissue type, the dosage and the treatment duration. This thesis also provides an alternative explanation for previously reported controversial findings where antioxidants (such as NAC) have exerted deleterious effects on health. Finally, the results of this thesis provide new insights into the appropriate design of antioxidant treatment studies: optimizing treatment dosage and duration may be the key to achieve success with antioxidant therapy.

Keywords: Adipocyte; Antioxidants; Browning; Reductive stress; Hormesis

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