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CONCEPTUAL CONTRIBUTION

Mitochondrial oxidative stress and inflammation: an slalom to obesity and insulin resistance

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Mitochondria, in addition to energy transformation, play a role in important metabolic tasks such as apoptosis, cellular proliferation, heme/steroid synthesis as well as in the cellular redox state regulation. The mitochondrial phosphorylation process is very efficient, but a small percentage of electrons may prematurely reduce oxygen forming toxic free radicals potentially impairing the mitochondria function. Furthermore, under certain conditions, protons can reenter the mitochondrial matrix through different uncoupling proteins (UCPs), affecting the control of free radicals production by mitochondria. Disorders of the mitochondrial electron transport chain, overgeneration of reactive oxygen species (ROS) and lipoperoxides or impairments in antioxidant defenses have been reported in situations of obesity and type-2 diabetes. On the other hand, obesity has been associated to a low degree pro-inflammatory state, in which impairments in the oxidative stress and antioxidant mechanism could be involved. Indeed, reactive oxygen species have been attributed a causal role in multiple forms of insulin resistance. The scientific evidence highlights the importance of investigating the relationships between oxidative stress and inflammation with obesity/diabetes onset and underlines the need to study in mitochondria from different tissues, the interactions of such factors either as a cause or consequence of obesity and insulin resistance.

Key words: Reactive oxygen species, Uncoupling proteins, Insulin, Weight gain.

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Mitochondria are double-membraned cell organelles that are specialized in converting energy-yielding macronutrients into ATP via the process of oxidative phosphorylation (8). In addition to energy transformation, these cell structures also play a role in other important metabolic tasks such as apoptosis, cellular proliferation, heme/steroid synthesis as well as in the cellular redox state regulation (20).

The oxidative phosphorylation process is mediated by mitochondrial inner membrane reductase and oxidase proteins, which participate in the electron transport chain. The production of ATP is achieved by the oxidation of glycolysis products and fatty acids, where the tricarboxilic acid cycle is involved to produce energy-rich molecules containing electrons with a high transfer potential such a NADH and $FADH_2$ (20) The redox energy from NADH and $FADH_2$ is transferred to oxygen in several steps via the electron transport chain and the incremental release of energy is applied to pump protons outside the mitochondria matrix generating a strong electrochemical gradient across the inner membrane. The chemiostatic return of such protons to the matrix through the ATP synthase complex is used to synthesize ATP from ADP. Overall, this process is very efficient, but a small percentage of electrons may prematurely reduce oxygen forming toxic free radicals potentially impairing the mitochondria function. Furthermore, under certain conditions, protons can reenter the mitochondrial matrix through different uncoupling proteins (UCPs), which results in heat dissipation without contributing to ATP formation, but affecting the control of free radicals production by mitochondria (15) and eventually the energy conversion efficiency as demostrated after the ectopic expression of UCP1 by DNA transfer in mouse liver mitochondria (7).

In this context, it has been hypothesized that free radical production is dependent on resting metabolic rate, which is increased in situations of excessive weight-for-height and also that mitochondrial dysfunctions may be important in the production of free radicals and subsequent effects on obesity (4). Interestingly, it has been reported that adipose tissue and liver might play an important role in the development of oxidative stress during obesity. Thus, disorders of the mitochondrial electron transport chain, overgeneration of reactive oxygen species (ROS) and lipoperoxides or impairments in antioxidant defenses have been reported in diet-induced situations of obesity (12, 16). Also, a down-regulation of electron transport chain genes in visceral adipose tissue involving TNF-α have been described in type-2 diabetes (3) as well as in genes participating in the oxidative phosphorylation pathway in obese subjects as compared to lean individuals, being both high-fat consumers and with similar physical activity patterns (unpublished results). Additionally, it has been demonstrated that a high-fat diet orchestrated down-regulates genes required for mitochondrial oxidative phosphorylation in skeletal muscle (17).

The specific assessment of mitochondrial oxidation by obese volunteers as compared to lean controls through the 2-keto [1-^{13}C] isocaproate breath test before and after weight loss revealed differences in the mitochondrial function, which provide reinforcing data to be considered in understanding the involvement of mitochondria and oxidative stress in the etiology of obesity (14). Also, subjects carrying different UCPs gene polymorphisms

might be differently prone to suffer from overweightness (1).

In this context, a few reports have argued in favor of an altered oxidative redox state in accumulated fat as assessed by H_2O_2 generation and malondialdehyde (MDA) is the triggering mechanisms of obesity (5, 13). These findings are complemented with the observation that an adiposity reduction was induced by ascorbic acid supplementation in a cafeteria model of obesity (2). Furthermore, antioxidants such as vitamin E, N-acetylcisteine, lipoic acid, betain have been proposed to be beneficial in the treatment of oxidative stress related diseases (11).

In support of the previous studies, the activation of monoamine oxidase and semicarbazide sensitive amine oxidase by exogenous substrates produce hydrogen peroxide, which exhibits insulin like properties and inhibition of lypolisis as described in human adipose tissue (21). Intriguingly, an increase in glutathione content and a decrease in the redox state by antioxidant treatment promoted the accumulation of triglycerides in preadipocytes (6). These different outcomes could be in part reconciled by the fact that doses, tissues, experimental conditions and compensatory homeostatic mechanisms should be taken into consideration to interpret the distinct approaches, but also by admitting that much is still unknown and remains to be elucidated.

On the other hand, obesity has been associated to a low degree pro-inflammatory state, in which impairments in the oxidative stress and antioxidant mechanism could be involved by affecting transcriptional factors such as NFK_β being activated by ROS generation or mediated by TNF-α. Indeed, reactive oxygen species have been attributed a causal role in multiple forms of insulin resistance (9),

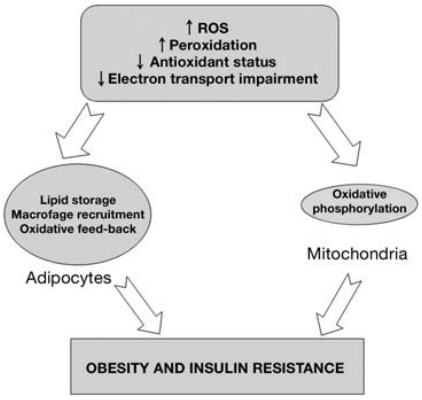

Fig. 1. *Processes concerning the interactions of mitochondrial oxidative stress and inflammation with influence on obesity and insulin resistance features.*

while a paracrine loop between adipocytes and macrophages may contribute to aggravate inflammatory changes by means of FFA and TNF-α (18). The recent finding that this adipokine impairs mitochondrial biogenesis and function in different tissues of obese rodents by downregulating eNOS expression suggest a novel pathophysiological process that sustains obesity mediated by mitochondrial affectation (19), which could be better interpreted by considering the aforementioned statements and experimental data. These findings are reinforced by observations demonstrating an oxidative burden in prediabetic and diabetic subjects as revealed by changes in plasma coenzyme Q (10).

The previous scientific evidence is not at all conclusive, but highlights the importance of investigating the relationships between oxidative stress and inflammation with obesity/diabetes onsets and underlines the need to study in mitochondria from different tissues, the interactions of such factors either as a cause or consequence of obesity and insulin resistance (Fig. 1).

J.A. MARTÍNEZ. *Estrés oxidativo mitocondrial e inflamación: papel en la obesidad y resistencia insulínica.* J. Physiol. Biochem., **62** (4), 303-306, 2006.

Las mitocondrias, además de participar en la obtención de energía a partir de nutrientes, juegan un papel relevante en diversas rutas metabólicas como la apoptosis, proliferación celular y síntesis de esteroides junto con la regulación del estado redox celular.

La fosforilación oxidativa es un proceso muy eficiente, pero un pequeño porcentaje de electrones podrían prematuramente reducir radicales libres, los cuales pueden afectar a la función mitocondrial. Además, bajo ciertas condiciones, los protones pueden penetrar en la matriz mitocondrial a través de las proteínas desacoplantes (UCPs), afectando al control de la producción de radicales libres por las mitocondrias. Determinadas alteraciones de la cadena de transporte de electrones, así como la sobreproducción de especies reactivas al oxígeno y lipoperóxidos o alteraciones en la capacidad defensiva antioxidante están siendo descritas en situaciones de obesidad y diabetes tipo II. Por otra parte, la obesidad se asocia con una situación proinflamatoria de bajo grado, donde desequilibrios entre el estrés oxidativo y los mecanismos antioxidantes pueden estar implicados. Ciertamente, especies oxígeno–reactivas pueden participar en algunas formas de resistencia a la insulina. Las evidencias científicas actuales subrayan la importancia de investigar las relaciones entre el estrés oxidativo y la inflamación con la obesidad y la diabetes así como la participación de las mitocondrias en diferentes tejidos y sus interacciones como causa o consecuencia de la excesiva ganancia de peso y la resistencia a la insulina.

Palabras clave: ROS, Proteínas desacoplantes, Insulina, Ganancia de peso

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