EFFECT OF BIOACTIVE COMPOUNDS AND ENVIRONMENTAL POLLUTANTS ON HEPATIC METABOLISM AND MITOCHONDRIAL FUNCTION

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Background

Liver is the main organ involved in response to both dietary lipid handling and toxic injury and mitochondria play a key role in cellular adaptation in response to nutritional and environmental stress conditions. Their dysfunction has been related to obesity-related metabolic diseases, such as insulin resistance and non-alcoholic fatty liver disease. Mitochondria are dynamic organelles that frequently undergo fission and fusion processes, and imbalances in these processes may be also involved in metabolic diseases. Different bioactive compounds have been shown to improve mitochondrial function and dynamic behaviour, counteracting cellular damage and metabolic diseases. We recently reviewed the effect of different dietary fat source and the role of omega 3 polyunsaturated fatty acids (PUFA) on mitochondria function/

dynamic behaviour and endoplasmic reticulum (ER) stress in metabolic diseases (Putti et al., Front Physiol. 2015; Putti et al., Front Physiol. 2016; Lepretti et al. Nutrients, 2018; Sergi et al., Front. Physiol. 2019). Moreover, environmental chemicals can be introduced by consuming contaminated foods and their physiological impact on hepatic metabolism and mitochondrial function is poorly understood. Based on these evidences, our aim is to focus on the impact of persistent organic pollutants as well as bioactive compounds (namely unsaturated/polyunsaturated fatty acids and polyphenols) on mitochondrial function/efficiency and dynamic behaviour as well as on oxidative stress, ER stress and inflammatory/apoptosis pathways in hepatic metabolism impairment.

Main achievements

We obtained results on physiological adaptation to environmental pollutants as well as to high fat diet rich in lard (saturated fatty acid) or fish oil (polyunsaturated fatty acids), on cellular metabolism and mitochondrial function/dynamic behaviour in experimental animal model. We showed that high-lard (HL) diet elicited high hepatic lipid accumulation and insulin resistance associated with mitochondrial dysfunction, oxidative stress and a shift towards mitochondrial fission processes, whereas high-fish oil (HFO) diet had an anti-steatotic effect associated with increased mitochondrial fusion processes in Wistar rats (Lionetti et al. Plos One 2014). We also showed that dietary fat sources may differentially affect the development of inflammation in insulin-sensitive tissues during chronic overfeeding (Lionetti et al. Int J Mol Sci. 2014). Moreover, HFO diet induced less testicular histology impairment, oxidative stress, and apoptosis compared to a HL diet. This finding was associated with an increase in antioxidant activities and a shift toward mitochondrial fusion processes induced by HFO compared to HL diet, suggesting that ω3-PUFAs may act as bioactive compound targeting mitochondria dynamics also to prevent testicular impairment (Migliaccio et al, Int J Mol Sci. 2019). Noteworthy, we also found that the environmental chemical dichlorodiphenyldichloroethylene (DDE), a persistent metabolite of dichlorodiphenyltrichloroethane (DDT), can affect mitochondrial function in testis and liver in rat model. DDE produced cellular stress leading to antioxidant impairment and apoptosis, associated with tissue damage in testis (Migliaccio et al, Cells 2019). Moreover, xenobiotic exposure induced hepatic oxidative stress and we suggested that mitochondrial UCP2 induction could be an adaptive response to limit excessive oxidative damage, mainly in condition of xenobiotic exposure (Migliaccio et al., Environ Toxicol 2019; Migliaccio et al., Plos one 2019).

Future perspectives

In the light of our previous results on bioactive compounds (mainly omega-3

polyunsaturated fatty acids vs. saturated fatty acids) and environmental pollutants (mainly DDE) on mitochondrial function and cellular stress in in vivo animal models, we will focus our future researches on the studies of interaction of mitochondria with ER stress and apoptosis induction in an "in vitro" model. We will evaluate dose- and time-dependent effects of environmental pollutant DDE and bioactive compounds (monounsaturated fatty acids, omega-3 PUFA and olive oil polyphenols) alone or in combination in HEPG2 cells. Mitochondrial function will be assessed by measuring oxygen consumption by Clark electrode. In particular, cytochrome oxidase activity as overall marker of mitochondrial activity (Lionetti et al., 2004) will be determined. Mitochondrial efficiency will be evaluated by determining uncoupling protein content. Mitochondrial dynamic behaviour will be assessed by western blot analysis of protein involved in mitochondrial fusion (mitofusin 2 and OPA1) and fission (Fis1 and DRP1) processes. Markers of oxidative stress, ER stress and apoptosis will be also assessed by western blot, PCR and spectrophotometric analysis. The results will be useful to clarify the complex cellular mechanisms and the cross talk between mitochondria and other cellular organelles underlying physiological adaptation both to environmental pollutants and bioactive compounds. The results could be useful to find possible common cellular pathway involved in the cellular adaptation to environmental stressors and in the etiopathogenesis of nutritional-induced metabolic diseases, as well as to define new targets for metabolic diseases prevention and therapy.

Publications

1. *Migliaccio V, Sica R, Di Gregorio I, Putti R, Lionetti L. (2019) High-Fish Oil and High-Lard Diets Differently Affect Testicular Antioxidant Defense and Mitochondrial Fusion/Fission Balance in Male Wistar Rats: Potential Protective Effect of ω3 Polyunsaturated Fatty Acids Targeting Mitochondria Dynamics. Int J Mol Sci. 25;20(12). pii: E3110. doi:10.3390/ijms20123110.*
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8. *Putti R, Sica R, Migliaccio V, Lionetti L. Diet impact on mitochondrial bioenergetics and dynamics. Front Physiol. 2015; 8;6:109.doi: 10.3389/fphys.2015.00109.*

9. *Lionetti L, Mollica MP, Donizzetti I, Gifuni G, Sica R, Pignalosa A, Cavaliere G, Gaita M, De Filippo C, Zorzano A, Putti R. High-lard and high-fish-oil diets differ in their effects on function and dynamic behaviour of rat hepatic mitochondria. PLoS One. 2014; 4;9(3):e92753.doi:10.1371/journal.pone.0092753.*

10. *Lionetti L, Mollica MP, Sica R, Donizzetti I, Gifuni G, Pignalosa A, Cavaliere G, Putti R. Differential effects of high-fish oil and high-lard diets on cells and cytokines involved in the inflammatory process in rat insulin-sensitive tissues. Int J Mol Sci. 2014; 20;15(2):3040-63. doi:10.3390/ijms15023040.*

External collaborations

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