Lifestyle Genomics

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DOI: 10.1159/000517609

Published online: June 29, 2021

Proceedings from the

# 4th European Summer School on Nutrigenomics (ESSN 2021)

June 21–25, 2021

Guest Editor
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## Glucocorticoid Signaling Alterations Induced by Late-Onset Dietary Resctriction Aggravate Metabolic Inflammation in the Liver of Old Wistar Rats

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**Objectives:** Dietary restriction (DR) is the approach often used to delay the development of age-related disorders. One of the unresolved questions is how late beginning and short duration of DR affects disturbed metabolic balance caused by ageing. Glucocorticoid hormones have significant role in the regulation of energy metabolism and inflammation, especially during ageing when their systemic concentration arise. The aim of this study was to examine the impact of glucocorticoid signaling alterations induced by the late-onset DR on metabolic inflammation in the liver of old Wistar rats.

**Methods:** The experiments were conducted on 6- and 24-month-old male Wistar rats on *ad libitum* diet and 24-month-old animals on restrictive diet (60% of *ad libitum* daily intake) from 21$^{st}$ to 24$^{th}$ month (late-onset DR). The gene expression of proinflammatory cytokines was measured by qPCR, while protein levels of nuclear factor κB (NFκB) and antioxidant enzymes were determined by Western blot. Glucocorticoid signaling was analyzed at the level of glucocorticoid prereceptor metabolism and subcellular distribution of glucocorticoid receptor (GR). Liver corticosterone concentration was measured by ELISA.

**Results:** Decreased levels of antioxidant enzymes observed during ageing were accompanied with augmented inflammation, characterized by increased nuclear NFκB protein level and higher expression of Toll like receptor 4 and TNFα. Corticosterone concentration in the liver of old rats was increased despite unchanged level of proteins involved in glucocorticoid prereceptor metabolism. Late-onset DR reduced adipose tissue and liver mass of old animals, and further stimulated inflammation in the liver. Decreased level of hepatic corticosterone after DR was a consequence of increased expression of 5α-reductase which was in agreement with the decreased GR protein level in the nuclear fraction.

**Conclusion:** Late-onset DR did not improve expression of antioxidant enzymes and led to progression of age-related inflammation in the liver. This was accompanied with decreased levels of corticosterone and GR in the nucleus implying that late-onset DR aggravates inflammatory response through decreased glucocorticoid signaling in the liver of old rats.

**Acknowledgements:** This study was supported by Ministry of Education, Science and Technological Development of Republic of Serbia under Grant 451-03-68/2020-14/200007.

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## Impact of Cocoa/Methylxanthines Supplementation on Liver Glutathione Level in Aged Mice

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**Objectives:** Redox imbalance is one of the main features that characterize aging process, and strongly affects human metabolism. It has been confirmed that age-initiated reactive oxygen species formation and particularly increased liver sensitivity to oxidative damage can lead to various diseases. The causes of such events are, among others, changes in enzyme activity and redox substrate concentration on the hepatocyte antioxidant protection. The goal of this study was to appraise cocoa/methylxanthines prevention of hepatocyte glutathione depletion in aged healthy C57BL/6 male mice.

**Methods:** Animals in intervention group were treated by six months supplementation with cocoa powder or methylxanthines at quantity equivalent to human daily cocoa powder dose of 7.3 g. The activity of liver antioxidant enzymes, glutathione peroxidase (GSH-Px) and glutathione reductase (GR), as well as the glutathione and GSH-Px protein content were measured in both the control and intervention group.

**Results:** Concerning GSH-Px activity, a slightly increase was observed in mice supplemented with methylxanthines compared to control and cocoa group, but statistically significant difference was absent. It is interesting that the same group had a significant increase in GSH-Px protein level. This finding indicates that hepatocytes regulate activity of this enzyme post-translationally, i.e. activity is not affected by increased protein level. Glutathione content and glutathione reductase activity were not altered due to mentioned dietary interventions.

**Conclusions:** The obtained results indicate that liver antioxidant enzymes are very complexly regulated on transcriptional, translational and post-translational levels, and it could be assumed that a certain post-translational modification appears reducing the synthesized GSH-Px protein activity.

**Acknowledgements:** This research was supported by the Ministry of Education, Science and Technological Development of Serbia (451-03-9/2021-14/200161).

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## Nucleic Acids - Underrated Food Components

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One of the basic components of every cell are nucleic acids, which play key role in coding and synthesis of proteins as well as in regulation of many metabolic processes. Most research on