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High-fat diet leads to key hepatic miRNAs modulation that may drive lipid accumulation in liver that preceds insulin resistance in male mice

Carolina Panzarin*, Laís A. de P. Simino, Mariana C. S. Mancini, Marina F. Fontana, Letícia Martins Ignácio-Souza, Marcio A. Torsoni, Marciane Milanski, Adriana S. Torsoni.

Abstract
High-fat diet (HFD) consumption can lead to Non-Alcoholic Fatty Liver Disease (NAFLD), which is characterized by hepatic triglycerides accumulation and is directly associated with the prevalence of obesity in worldwide. Insulin resistance underlies the genesis of both obesity and NAFLD. These mecanisms can be regulated by microRNAs, such as miR-122 and Let-7 in the liver. Therefore, the aim of the present study was to investigate a possible connection between insulin resistance, obesity, NAFLD development and alterations in miR-122 and Let-7 expression in mice fed a HFD.

Key words:
High-fat diet, non-alcoholic fat liver disease, miRNAs.

Introduction

Insulin resistance underlies the genesis of obesity and NAFLD. Both diseases are directly associated and as obesity grows in worldwide, the prevalence of NAFLD also increases. Studies have shown that high-fat diet (HFD) consumption can lead to these conditions, and as the mechanism has not been fully elucidated microRNAs expression has been linked as possible regulators of those events. The most expressed miR in the liver, miR-122 is known to regulate lipid metabolism. Let-7 is also an important hepatic miR and recent studies have been showing that it is involved with glucose homeostasis and insulin sensitivity. Therefore, the aim of the present study was to investigate a possible connection between insulin resistance, obesity, NAFLD development and alterations in miR-122 and Let-7 expression in mice fed with an HFD.

Results and Discussion

Male Swiss mice were fed with either a control diet or an HFD. Animals fed an HFD were divided in groups, according to the days of the diet exposure: 1, 3, 7, 15, 30 or 56 days. Body weight, adiposity and serum CHOL were gradually increasing from day 7 to 56 (HF7 to HF56). Hepatic TAG level was higher in HF group and had an increase tendency since HF1 and continued to increase until HF56. For histologic analysis, it was observed that lipid accumulation appears on the first day of HFD (HF1), even after glycogen reduction in this tissue that occurred in HF3. Hepatic miR-122 expression was decreased from HF3 until HF56, and its predict target, Agpat, was higher than control with acute and chronic exposure to HFD, showing a negative correlation. Let-7 showed an increase at HF1, returned to normal levels at HF3 and was upregulated with a chronic exposure to the HFD, at HF56. Prkaa2 (AMPK), a predicted target of Let-7, was negatively modulated at HF1 and HF56, as expected.

We showed here that HFD consumption could alter miRNA expression pattern that may drive alterations in whole body homeostasis and disrupt metabolic syndrome phenotype since the first day of exposure. Hepatic miRNAs are reported to be involved in fat deposition within the liver, high levels of TAG and cholesterol in serum and hyperglycemia. miR-122 and Let-7, for example, have been showing important roles in lipid and glucose metabolism. In addition, it was seen in the liver that lipid accumulation appears first than glycogen reduction, making possible the hypothesis that insulin resistance may come after a stimulus of fat deposition from HFD.

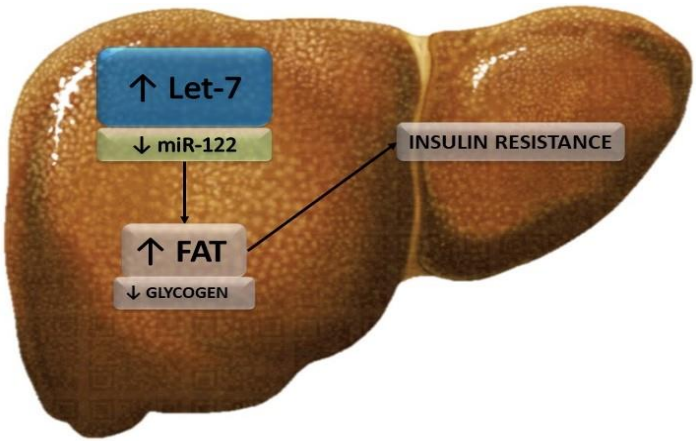

Image 1. High-fat diet leads to fat accumulation in liver. miRNAs modulation may drive lipid accumulation and after insulin resistance.

Conclusions

High-fat diet consumption can lead to hepatic microRNAs modulation that consequently, may be responsible for homeostasis alterations and enzymes expressions modifications related to lipid and glucose metabolism as the days exposed of HFD increased. Therefore, these alterations were reflected in animals phenotype, with increase in weight gain and adiposity. In addition, it seems that hepatic lipid accumulation can be the first change to occur, even before insulin resistance.

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