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The role of hepatic and adipose tissues cyclic adenosine monophosphate during the development of experimental non alcoholic fatty liver

Thesis

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Declaration

I declare that this **thesis** has been composed by myself and that this work, which has been recorded here in after has been done by myself. It has not been submitted for a **degree** at this or any other university.

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Dedication

I would like to dedicate this thesis with all my love to my family and for all my friends and those from whom I have learned, whenever and wherever they are.

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In
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Arabic abstract .....

Abstract

The role of hepatic and adipose tissues cyclic adenosine monophosphate during the development of experimental non alcoholic fatty liver. *Ashraf Khaled Mahmoud Awaad, Biochemistry Department, Faculty of Science, Ain Shams University.*

Non-alcoholic fatty liver disease (NAFLD) has emerged as the most common chronic liver disease in developed countries due to the increasing incidence of obesity and diabetes. The pathogenesis of NAFLD is multi-organs in which many organs are participated with the liver and adipose tissues are of central importance. Two types of adipose tissue can be distinguished, which have essentially antagonistic functions. Whereas white adipose tissue (WAT) stores excess energy as triglycerides, the function of brown adipose tissue (BAT) is to dissipate energy through the production of heat. Cyclic adenosine monophosphate (cAMP), a key second messenger molecule, is one of the most promising pathways that regulates various cellular functions including lipid and carbohydrate metabolism, inflammation, cell differentiation and tissue regeneration. cAMP induce gene transcription through activation of cAMP-dependent protein kinase (PKA), and consequently phosphorylation of the transcription factor cAMP response element-binding protein (CREB). CREB activity is strictly regulated by the level of the inducible cAMP early repressor (ICER), a natural antagonist that contains neither activating nor repressing domains. **Objective:** The present study was aimed to evaluate the role of hepatic, white and brown adipose tissues cAMP in the development of experimental NAFLD in an attempt to clarify the pathogenesis of the disease.

Methods: The experimental rats were divided into two groups (35 each): control group which fed a standard diet, and NAFLD group that fed a high fat diet (HFD) for 14 weeks. The blood was collected for serum separation then stored at −80°C, for future biochemical analysis. The whole liver, WAT and BAT were immediately removed and weighed. One lobe of liver from each animal was removed for histological assessment; the remaining lobes as well as adipose tissues were stored at −80°C, for cAMP and CREB quantification by ELSA kits and ICER expression by reverse transcriptase polymerase chain reaction (RT-PCR).

Results: The highest content of cAMP and CREB were detected in BAT of the control rats. However, NAFLD rats revealed a remarkable elevation in cAMP and CREB levels in the liver and WAT, while cAMP and CREB levels in BAT decreased to be 6.18 and 28.62 fold control value, respectively. On the other hand, ICER gene expression in the liver and WAT was downregulated in NAFLD rats, compared to control rats, however, NAFLD rats showed about 1.72 fold upregulation of ICER gene expression in BAT compared to control.

Conclusion: We conclude that cAMP pathway is complex and greatly influenced by numerous factors such abundance, localization and repression. Also, our results indicate that cAMP pathway provides an early signal in the progression to NAFLD representing a promising therapeutic target for the treatment of the disease.

Keywords: NAFLD, cAMP, CREB, CREM, ICER, AC, PKA, WAT, BAT