Study of inflammation mediated by lipids in a Microglia Cell Model to deepen into brain dysregulation by obesity

Salsinha, AS[1,2], Rodrigues, A[2], Socodato, R[2], Relvas, JB[2], Rodríguez-Alcalá, LM[1], Pintado, ME[1]

1. Universidade Católica Portuguesa, CBQF - Centro de Biotecnologia e Química Fina –Laboratório Associado, Escola Superior de Biotecnologia, Rua de Diogo Botelho, 1327, 4169-005 Porto, Portugal
2. Instituto de Investigação e Inovação em Saúde and Instituto de Biologia Molecular e Celular (IBMC), Universidade do Porto – Rua Alfredo Allen, 208, 4200-135 Porto, Portugal

Introduction

Obesity has currently reached a worldwide pandemic level, being responsible for the development of non-communicable diseases. The strategies for body weight control have been targeting mainly adipose tissue. Nevertheless, several investigations suggested that brain plays a major role in obesity development: saturated fatty acids (SFAs) bind to TLR-2 and -4 in the hypothalamus, triggering inflammatory processes resulting in overconsumption and food addiction. Some concerns arise here since the current western diet, associated with high-fat and -fructose consumption, often provides considerable amounts of SFAs.

On the other hand, omega 3 from fish oils has reported as an activator of GPR120 and its anti-inflammatory effects involve the inhibition of the phosphorylation of the inhibitory subunit of NFkB: IkB. In addition, both CLA and CLNA (punicic acid) isomers have shown to increase lean body mass and to reduce body fat mass in animal models. Their anti-inflammatory action was reported to be mediated by PPAR γ and σ induction.

Objectives

Despite promising results regarding a potential beneficial effect of CLA and CLNA isomers in obesity, namely on the peripheral tissues, few studies have specifically targeted the antiobesogenic effect of these isomers in hypothalamus inflammation.

Microglia is the main cellular component of the brain innate immune system and a key player in both regulation and protection of the central nervous system homeostasis. Therefore, excessive activation of microglia and inflammation-mediated neurotoxicity are implicated in the progression of several neurological disorders.

This work aimed to analyze a human microglia cell line activation by a solution mimicking the western pattern diet (palmitic acid, a SFA, and fructose), specifically targeting the NFkB pathway. Furthermore, by performing a pre-incubation of the cell cultures with omega 3, CLA and CLNA isomers prior to the western pattern diet solution exposure, their preventive anti-inflammatory effect was assessed.

Methods and Results

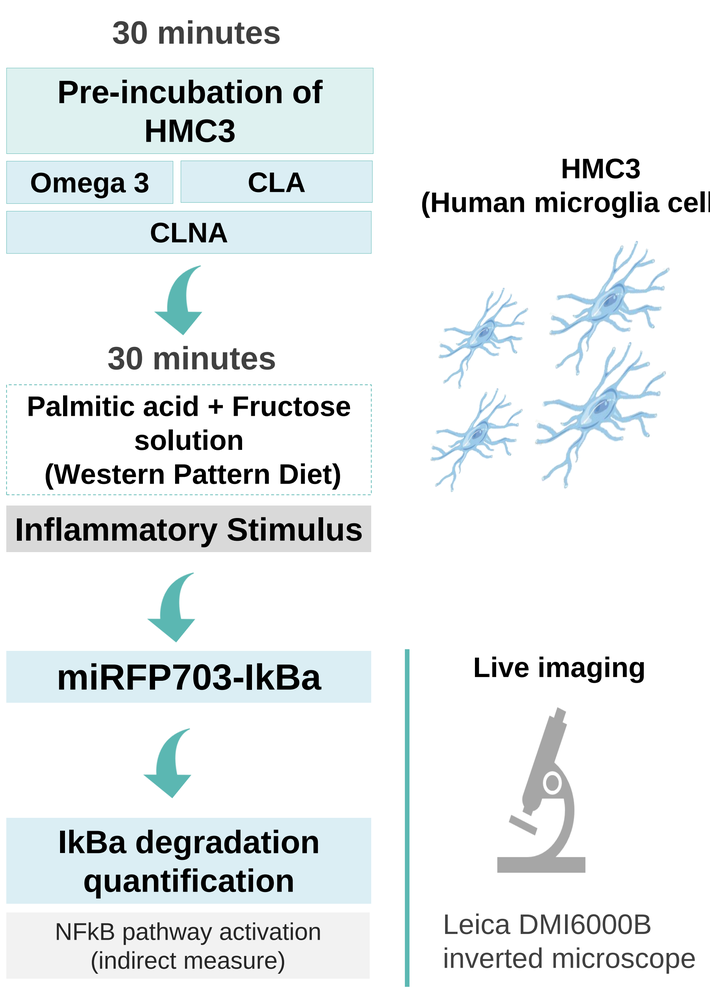

Figure 1. Experimental design schematic representation.

Table 1. Composition of the tested Fatty acids solutions.

Solution ID	Fatty acids	Other Components	Proportion	Final concentration (per solution)
Inflammatory Stimulus (western pattern diet)	Palmitic Acid (C16:0)	Fructose	2:1	**100 µM**
Omega 3	EPA (C20:5 n-3) DHA (C22:6 n-3)	- -	1:1	
CLA	Rumenic acid (C18:2 *c*9*t*11) C18:2 *t*10*c*12 CLA isomer	- -	1:1	
CLNA	Punicic Acid C18:3 *c*9*t*11*c*13	-	-	

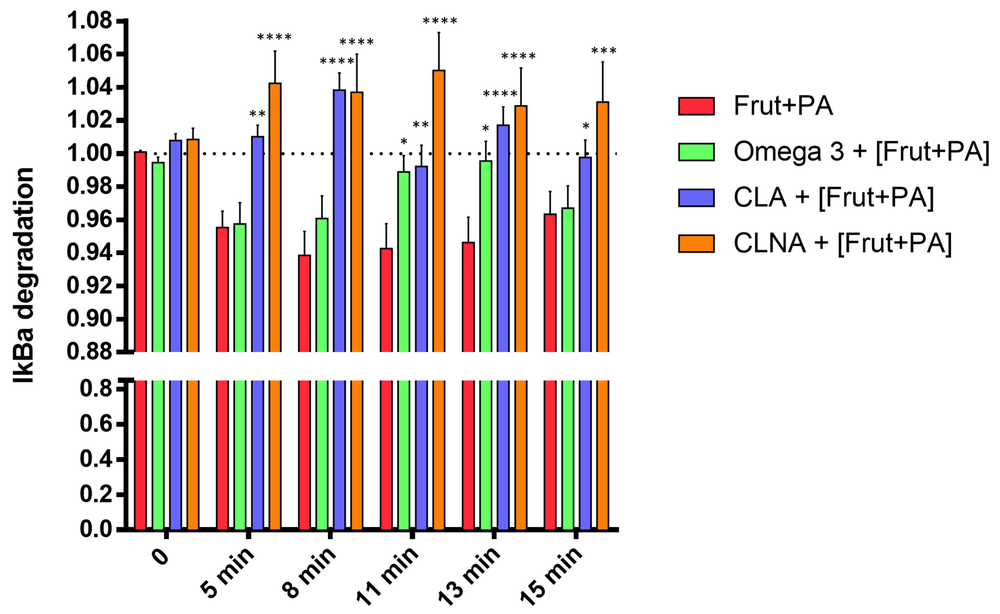

Figure 2. CLNA, CLA and omega 3 fatty acids prevent NFkB pathway activation by Fructose and Palmitic acid. Results of the quantification of human microglia expressing the miRFP703-IkBa sensor for the selected time points (0, 5, 8, 11, 13 and 15 minutes). Error bar represents the SEM calculated from >10 cells from three independent cultures. Two-way ANOVA in relation to Frut+PA, where no pre-incubation with the selected fatty acids was performed. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Conclusions

The incubation of the human microglia cell line cultures with the solution mimicking the western pattern diet (Fructose+Palmitic acid) showed an activation of the NFkB pathway by a significative IkBa degradation (decreased signal). By pre-incubating the cells with individual omega 3, CLA and CLNA solutions, the IkBa degradation was significantly lowered (increased signal) in comparison to cells where no pre-incubation was performed. Thus, these results point out to an anti-inflammatory effect of CLNA, CLA and omega 3 fatty acids under the studied conditions. Surprisingly, for the first time the most promising anti-inflammatory potential was obtained for conjugated fatty acids (CLA and CLNA). Even though omega 3 is widely studied for its promising anti-inflammatory potential, few studies have reported CLA and CLNA isomers anti-inflammatory effect at the central nervous system level.

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