Palmitic acid enhances TLR4 expression and promotes resistin/TLR4 signaling

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Introduction / Aim

Toll-like receptor 4 (TLR4) has a critical role in innate immunity, and the activation of inflammatory pathways plays an important role in the induction of insulin resistance. Indeed, we have recently reported that TLR4 is implicated in resistin-induced inflammation and insulin resistance in the hypothalamus (1). We also show that TLR4 is up-regulated in the hypothalamus of mice fed a high-saturated fat diet. **Here, we explore the molecular mechanism implicated in the regulation of TLR4 expression**. For this purpose, human neuroblastoma cells (SHSY-5Y) were exposed during 4h to either the saturated fatty acid palmitic acid or the omega-3 polyunsaturated fatty acid docosahexaenoic acid (DHA), and then challenged for resistin.

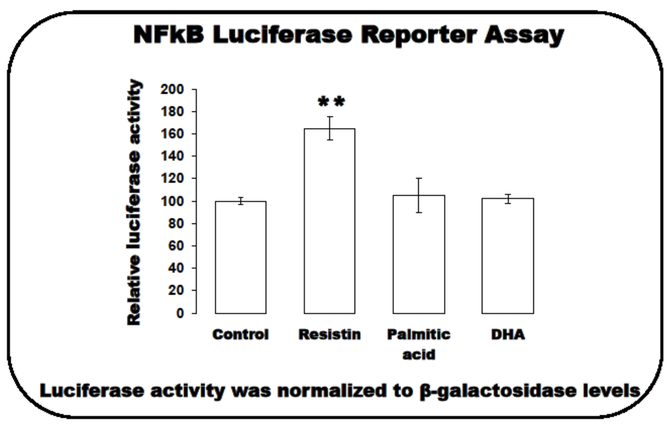
Materials & Methods

Serum starved SHSY-5Ywere incubated for 4h in the presence or the absence of palmitic acid (200 µM), DHA (20 µM) or resistin (200 ng/ml). Then, total RNA and proteins were prepared for adequate analyses in order to evaluate the impact on the expression of TLR4 and inflammatory markers.

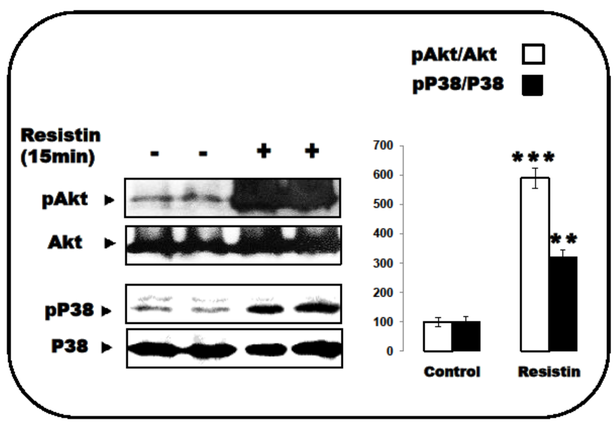
Protein and RNA analysis: Solubilized proteins were subjected to Western blot using adequate antibodies and the total RNA was used in quantitative RT-PCR using adequate primers

Results

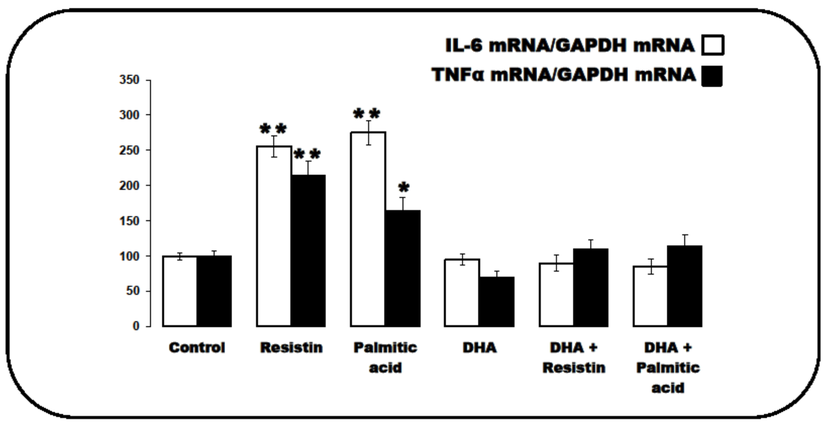
Resistin treatment increases NFkB activation



Resistin induces phosphorylation of Akt and P38 MAPK

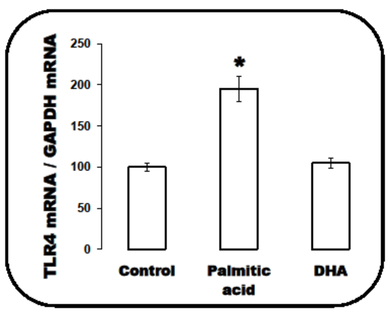


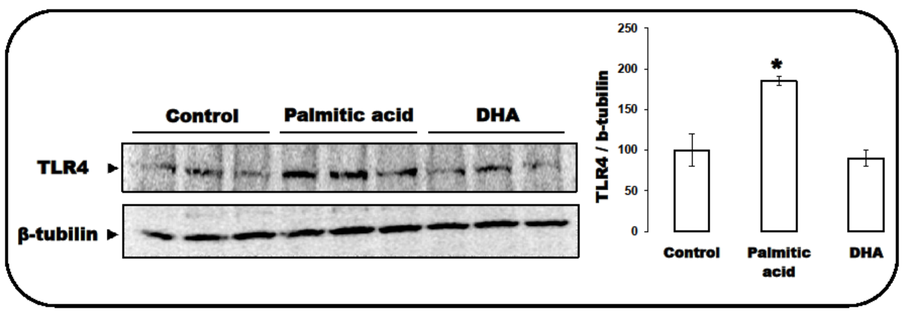
DHA suppresses palmitic acid and resistin induced up-regulation of IL-6 and TNF-α

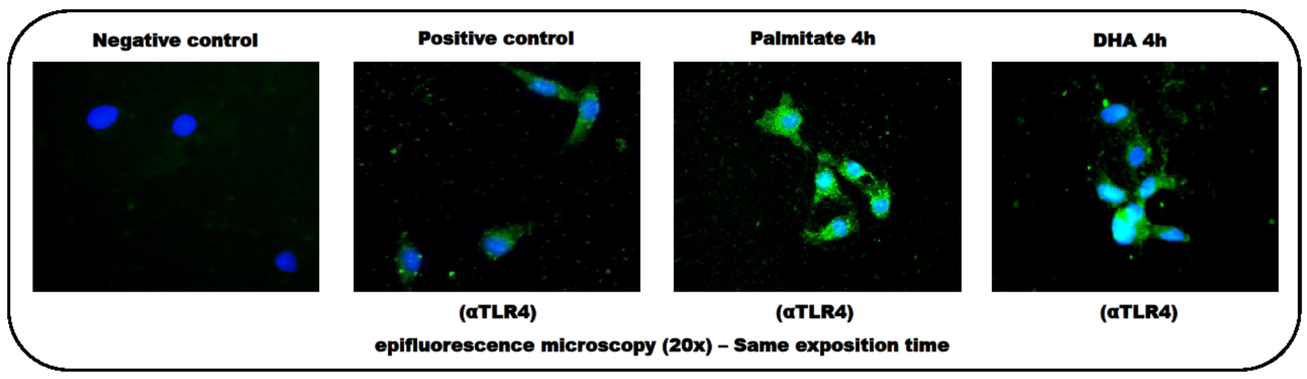


We analyzed the effect of resistin, palmitic acid and DHA on inflammation markers. We show that resistin was able to activate NF-κB and to increase Akt and p38 MAPK phosphorylation. In addition, resistin and palmitic acid upregulate both IL-6 and TNF-α. Interestingly, this effect is completely abolished by DHA treatment.

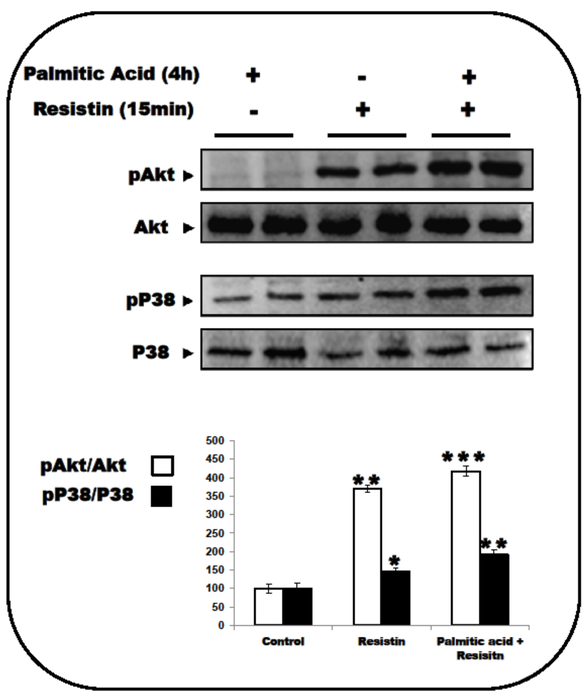
Palmitic acid pretreatment increases TLR4 expression

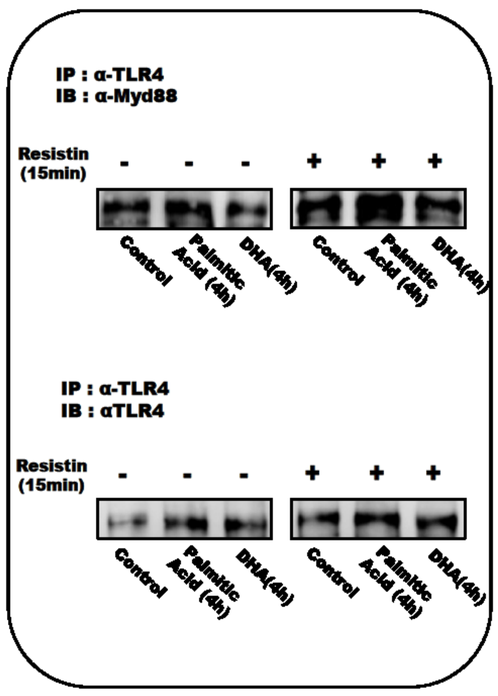






Palmitic acid potentiates resistin effects and promotes resistin/TLR4/Myd88 signaling





We studied the possible synergistic interaction between resistin and palmitic acid. Our results show that palmitic acid but not DHA pretreatment increases TLR4 expression, at the protein and mRNA levels. Importantly, palmitic acid pretreatment potentiates resistin effects and promotes resistin/TLR4/Myd88 signaling.

Conclusion

In conclusion, we show in neurons that :1/ palmitic acid induces TLR4 expression, 2/ palmitic acid amplifies resistin pro-inflammatory effects, 3/ DHA treatment overcomes both resistin and palmitic acid pro-inflammatory effects.

Reference

(1) Central resistin overexposure induces insulin resistance through Toll-like receptor 4. **Benomar Y**, Gertler A, De Lacy P, Crépin D, Ould Hamouda H, Riffault L, Taouis M. Diabetes. 2013

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