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Corticotropin Releasing Factor Affects the Expression of TLR4 Receptor in Adipocytes

Eirini Dermitzaki[1], Ariadne Androulidaki[1], Christos Tsatsanis[1], Achille Gravanis[2], Andrew N. Margioris[1]

Departments of Clinical Chemistry-Biochemistry[1] and Pharmacology[2], School of Medicine, University of Crete, Heraklion, Greece

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S u m m a r y. Obesity is associated with chronic systemic low grade inflammation as well as inflame-mation of adipose tissue with ad hoc accumulation of macrophages. Like macrophages, the adipocytes have the ability to detect circulating lipopolysaccharides (LPS) via toll-like receptos-4 (TLR4) and produce inflammatory cytokines. Human adipocytes also ex-press the corticotrophin-releasing factor (CRF) family of neuropeptides and their receptors, a system affecting innate immunity at the level of macrophages. Aim of the present study was to examine the effects of CRF on the immune phenotype of adipocytes and specifically on their expression of the TLR4 receptor.

INTRODUCTION

Obesity is associated with constant low level systemic inflammation as well as an ongoing inflammation within the visceral adipose tissue.

In obesity, adipocytes produce chemotactic factors which attract monocytes/macrophages from the blood stream. Upon entering the adipose tissue, monocytes are activated to macrophages which further activate adipocytes to produce more chemotactic factors and pro-inflammatory cytokines.

Lipo-poly-saccharide (LPS) stimulates macrophages, via the TLR4 receptor, to produce pro-inflammatory mediators (1). Interestingly, the expression levels of TLR4 control macrophage sensitivity to LPS. LPS transiently downregulates TLR4 promoting macrophage tolerance to further LPS stimulation while, the stress-related peptide corticotrophin-releasing factor (CRF) augments the efffect of LPS by inducing TLR4 gene expression in macrophages.

Adipocytes and macrophages share several common characteristics including the TLR4-NFkB-pro-inflammatory cytokine cascade. Furthermore, adipocytes and monocytes have a common precursor cells.

A complete CRF system exists within the visceral adipose tissue consisting of CRF, the Urocortins (UCNs), and their receptors CRF1 and CRF2 (2,3).

The aim of the present work was to examine the effect of CRF and CRF-related peptides in the production of adipogenic peptide Leptin and the pro-inflammatory cytokines (IL6, IL8) as well as the expression levels of TLR4 in adipocytes.

MATERIALS

We have used the mouse 3T3L1 pre-adipocyte cell line both as cultured pre-adipocytes and as fully differentiated adipocytes (4). Pre-adipocytes or fully differentiated 3T3L1 cells were incubated with CRF (10^{-8} M) and/or LPS (10 ng/ml) for 5h, 10h and 15h and levels of TLR4, Leptin, IL6 and IL8 were measured by FACS analysis, Real Time PCR or ELISA.

RESULTS

Our data show that 3T3L1 pre-adipocytes co-incubated for 5 or 10 h with CRF and/or LPS revealed a markedly decrease TLR4. In addition, fully differentiated 3T3L1 cells incubated with LPS plus CRF suppressed TLR4 by Real Time PCR.

CRF and UCN1 augmented LPS-mediated suppression of Leptin production from differentiated to adipocytes 3T3L1 cells.

CRF and the UCNs suppressed LPS-induced production of IL6 and IL8 from differentiated to adipocytes 3T3L1 cells.

DISCUSSION

LPS exerts a pro-inflammatory effect on differentiated 3T3L1 adipocytes suppressing the production of Leptin and inducing the production of the pro-inflammatory cytokines IL6 and IL8.

CRF1 and CRF2 receptor agonists exert a generalized suppressing effect on adipocytes suppressing their production of Leptin and of the pro-inflammatory cytokines IL6 and IL8.

CRF promotes TLR4 expression in undifferentiated adipocytes while it suppress its expression in differentiated adipocytes, suggesting that stress neuropeptides may have distinct effects on pre- and mature adipocytes.

In conclusion, CRF suppresses TLR4 expression in adipocytes, thus containing their pro-inflammatory activity.

REFERENCES

1. Hotamisligil G.S.: *Nature 444*: 860 (2006)
2. Seres J., et al.: *J. Clin. Endocrinol. Metab. 89*: 965 (2004)
3. Friedberg M., et al.: *J. Clin. Endocrinol. Metab. 88*: 385 (2003)
4. Gregoire F., et al.: *J. Physiol. Rev. 78*: 783 (1998)