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ScienceDirect
Progress in Lipid Research 46 (2007) 89–107
Progress in Lipid Research
www.elsevier.com/locate/plipres

Review

Leptin: At the crossroads of energy balance and systemic inflammation

Alexandre A. Steiner, Andrej A. Romanovsky *

Systemic Inflammation Laboratory, Trauma Research, St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013, USA

Received 20 October 2006; received in revised form 10 November 2006; accepted 16 November 2006

Abstract

In addition to playing a central role in energy homeostasis, leptin is also an important player in the inflammatory response. Systemic inflammation is accompanied by fever (less severe cases) or hypothermia (more severe cases). In leptin-irresponsive mutants, the hypothermia of systemic inflammation is exaggerated, presumably due to the enhanced production and cryogenic action of tumor necrosis factor (TNF)-α. Mechanisms that exaggerate hypothermia can also attenuate fever, particularly in a cool environment. Another common manifestation of systemic inflammation is behavioral depression. Along with the production of interleukin (IL)-1β, this manifestation is exaggerated in leptin-irresponsive mutants. The enhanced production of TNF-α and IL-1β may be due, at least in part, to insufficient activation of the anti-inflammatory hypothalamo–pituitary–adrenal axis by immune stimuli in the absence of leptin signaling. In experimental animals and humans that are responsive to leptin, suppression of leptin production under conditions of negative energy balance (*e.g.*, fasting) can exaggerate both hypothermia and behavioral depression. Since these manifestations aid energy conservation, exaggeration of these manifestations under conditions of negative energy balance is likely to be beneficial.

Keywords: Adipose tissue; Obesity; Leptin receptor; Lipopolysaccharide; LPS; Immune-to-brain signaling; Fever; Hypothermia; Sickness behavior; Behavioral depression; Anorexia

Contents

Abbreviations: HPA, hypothalamo–pituitary–adrenal; IL, interleukin; LPS, lipopolysaccharide; LR, leptin receptor; TNF, tumor necrosis factor; T_b, deep body temperature.

* Corresponding author. Tel.: +1 602 406 5059; fax: +1 602 406 4113.
E-mail address: aromano@chw.edu (A.A. Romanovsky).

0163-7827/$ - see front matter
doi:10.1016/j.plipres.2006.11.001

1. Introduction

Inflammation is an important host-defense response [1]. However, when the inflammatory response becomes overwhelming, it disrupts vital homeostatic processes and ultimately results in multiple organ failure and death [2]. It is not surprising, therefore, that severe forms of inflammation are major medical problems. A common complication in hospitalized patients is sepsis (systemic inflammation due to infection). Mortality rate is extremely high in septic patients: it ranges from 30% in those patients that do not develop shock to 70% in those patients that do [3–6]. Sepsis becomes an even more serious threat in view of the fact that its incidence is increasing fast, *i.e.*, at an annual rate of 9% in the United States [7]. The increasing incidence of sepsis seems to be associated with, among other factors, the escalating incidence of metabolic disorders, particularly obesity [8–10]. Clearly, understanding how the mechanisms involved in obesity (and energy homeostasis in general) affect systemic inflammation is important.

The adipocyte-derived hormone, leptin, plays a central role in energy homeostasis, and resistance to its actions is associated with obesity [11–13]. Since it also modulates inflammation [14,15], leptin may integrate energy balance and systemic inflammation. In the present article, we examine this issue. A succinct review

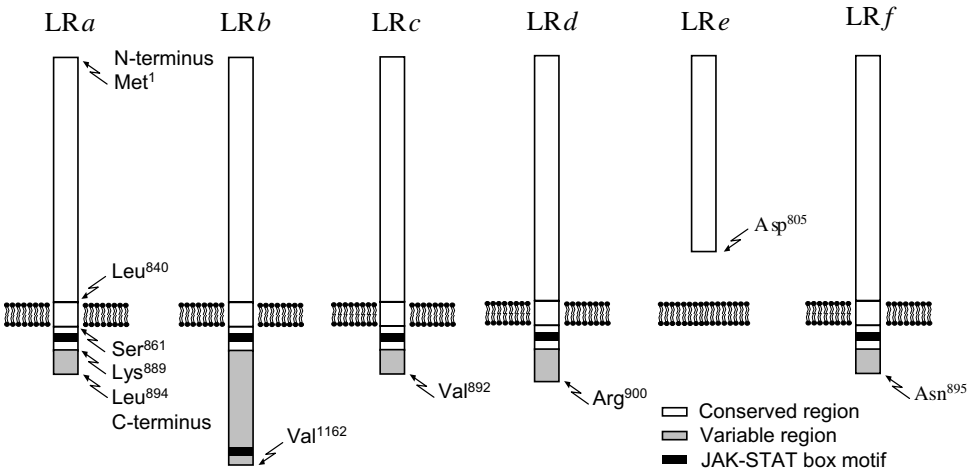

Fig. 1. Structures of LR isoforms. All isoforms are products of splicing variants of a single transcript. Each isoform has a conserved region, and may or may not have a variable region. The conserved region forms the extracellular and transmembrane domains as well as a small portion of the intracellular domain; the aminoacid sequence of this region is always constant, although it may be truncated. The variable region forms a large portion of the intracellular domain; the aminoacid sequence in this region is highly sensitive to splicing. The first or last aminoacid of each region and domain are listed at the first (left to right) diagram that contains this region or domain; amino acid numbering is based on the published sequences of mouse LR*a–e* [23,24] and rat LR*f* [25]. Box motifs for JAK-STAT phosphorylation are marked. Only when two JAK-STAT box motifs are present (as in LR*b*) does LR display full signal transduction capability.