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Leptin and aging: Review and questions with particular emphasis on its role in the central regulation of energy balance

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ABSTRACT

Leptin is produced mainly in the white adipose tissue and emerged as one of the key catabolic regulators of food intake and energy expenditure. During the course of aging characteristic alterations in body weight and body composition in humans and mammals, i.e. middle-aged obesity and aging anorexia and cachexia, suggest age-related regulatory changes in energy balance in the background. Aging has been associated with increased fat mass, central and peripheral leptin resistance as indicated by its failure to reduce food intake, to increase metabolic rate and thereby to induce weight loss. Leptin resistance is a common feature of aging and obesity (even in the young). The question arises whether aging or fat accumulation plays the primary role in the development of this resistance. The review focuses mainly on mechanisms and development of central leptin resistance. Age-related decline primarily affects the hypermetabolic component of central catabolic leptin actions, while the anorexigenic component is even growing stronger in the late phase of aging. Obesity enhances resistance to leptin at any age, particularly in old rats, calorie-restriction, on the other hand, increases responsiveness to leptin, especially in the oldest age-group. Thus, without obesity, leptin sensitivity appears not to decrease but to increase by old age. Interactions with other substances (e.g. insulin, cholecystokinin, endogenous cannabinoids) and life-style factors (e.g. exercise) in these age-related changes need to be investigated.

1. Introduction

Aging and obesity represent two world-wide public health burdens, both leading to severely impaired quality of life and increased morbidity of those affected. According to the prediction of the World Health Organization (WHO), by 2025 the global population of people aged 60 years and older will reach about 1.2 billion (mostly belonging to the early elderly or "transitional" phase up to 74 years of age, WHO, 2011; Rizzuto and Fratiglioni, 2014). By 2050 the world will have almost 400 million people aged 80 years or older (later elderly or old, WHO, 2012). Currently more than 10% of the world's adult population is obese [more than 1.4 billion adults are overweight, 500 million adults are obese (WHO, 2014)]. Moreover, aging and obesity are interconnected: on the one hand, middle-aged populations tend to become obese, on the other hand obesity accelerates aging and age-related degenerative processes (muscle atrophy, neurodegeneration). One of the common features of aging and obesity is a dysregulation of energy homeostasis (such as resistance to different regulatory peptides, leading to abnormalities of body weight and/or body composition) (Ahima, 2009; Carter et al., 2013), therefore the investigation of age- and nutritional state-related regulatory alterations are of outstanding importance.

In the past two decades, leptin as an adiposity signal has been gradually gaining a central place in studies of the regulation of energy balance and body weight. Leptin has a complex catabolic activity, i.e. it induces anorexia and enhances metabolic rate and body temperature (Sahu, 2004; Steiner and Romanovsky, 2007). Leptin exerts its catabolic actions mainly by altering the expression of neuropeptides in the arcuate nucleus of the hypothalamus: it enhances the activity of the catabolic melanocortin system, while it also suppresses that of the anabolic neuropeptide Y (NPY) and of the endogenous melanocortin antagonist agouti-related peptide (AgRP) (Baskin et al., 1999; Berglund et al., 2012). In addition, leptin also acts on different sites of the afferent vagus (gastric, intestinal, hepatic, portal branches or at the nodose ganglia, for references see Wang et al., 1997; Gaigé et al., 2002; Shiraishi et al., 1999; Buyse et al., 2001), transmitting information to the brainstem and the nucleus of the solitary tract (NTS) (Székely and Szelényi, 2005; Grill et al., 2002; Buyse et al., 2001).

Normally, leptin is produced mainly (though not exclusively) in the subcutaneous and to a lesser extent in the visceral white

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adipose tissue, together with other adipokines (Friedman and Halaas, 1998; Carter et al., 2013). Its production is stimulated by insulin (Ryan and Elahi, 1996), glucocorticoids (Masuzaki et al., 1997), thyroid hormones (Valcavi et al., 1997), estrogens, and inhibited by androgens (Watanobe and Suda, 1999). Additionally, leptin release has been detected in the stomach (Bado et al., 1998). Gastric leptin actions modulate local stretch sensing and gastric vagal afferent activity (Kentish et al., 2013). Leptin of gastric origin was also proven to bind to its receptors in the jejunum (Rasmussen et al., 2014). In the circulation most of it is bound to its soluble receptor, whereas a smaller fraction is in free form (Sinha et al., 1996). Circulating leptin was shown to activate hepatoportal sensors that, in turn, increase the sympathetic and suppress the parasympathetic outflow via reflex mechanisms (Niijima, 2011). In addition to these acute effects, long-term peripheral actions of the peptide are numerous, including beneficial effects on lipid and glucose metabolism and on insulin sensitivity. Low leptin levels are accompanied by high leptin sensitivity, by decrease in lipolysis and enhanced beta-oxidation of fatty acids – plasma triglyceride levels are low (Carter et al., 2013). Low triglyceride levels allow transport of leptin through the blood brain barrier and action of leptin into the hypothalamus and other structures of the brain (Banks et al., 2004). In the periphery, leptin may influence distribution of fat in the body as well as the functions of fat tissue(s) (Barzilai et al., 1997). Either or all of these steps may be altered during aging (Carter et al., 2013).

Earlier, the sensitivity to leptin has been shown to decline (with simultaneous hyperleptinemia) during the course of age-related weight gain and in obesity of any age and various etiologies (Myers et al., 2012). The combination of aging and obesity, i.e. age-related obesity is characterized by a tendency toward progressive weight gain starting at a younger age in humans and mammals. Such a weight gain is accompanied by the development of progressive peripheral and central leptin resistance (Scarpace et al., 2000a,b; Shek and Scarpace, 2000; Sahu, 2004). However, very old persons and mammals tend to lose body weight [aging anorexia, sarcopenia (Morley, 2001)] that cannot be connected with leptin resistance. The question arises whether age itself or rather the accompanying obesity determines the development of leptin resistance.

In view of other experimental data that describe improvement of leptin sensitivity in old rats following transient calorie-restriction, the hypothesis is raised that aging itself may not be a primary cause of leptin resistance in rodents (Fernández-Galaz et al., 2002). The present review focuses mainly on mechanisms and pathogenesis of central leptin resistance and on the analysis of the respective contribution of aging and body composition.

2. Potential mechanisms of leptin resistance

Following the identification of 16 kDa leptin in 1994 and the investigations of leptin deficiency in ob/ob mice (Zhang et al., 1994), later structural abnormalities of the peptide, its receptors (Chen et al., 1996) or resistance to its effects were analyzed. In view of the progressive aging of society and the exponential increase in the rate of human obesity, it is natural that there has been a great interest toward the possible role and mechanisms of action of this peptide.

Although leptin is produced in the periphery and has a number of peripheral actions too (in the liver, skeletal muscles, lungs, white or brown adipose tissue, etc.), as regards to the regulation of energy balance, its central actions appear to be more important (for reviews see Oswal and Yeo, 2010; Carter et al., 2013). From the circulation leptin can cross the blood-brain barrier (BBB) by a special saturable transport system (Banks et al., 1996) (that can be inhibited by plasma triglycerides in aging obesity), then it acts in various nuclei of the hypothalamus and in other extrahypothalamic tissues (Leinninger, 2009). Leptin binding on the long isoform of leptin receptor (LEPR-B) in the arcuate nucleus (ARC) influences the expression/activity of hypothalamic neuropeptides (melanocortins, NPY, etc.) and the function of second-order neurons of cerebral nuclei involved in energy balance (Schwartz et al., 1996a; Valassi et al., 2008). The LEPR-B detected in the ventral tegmental area (VTA) indicates a role for leptin in the mesolimbic dopaminergic reward system (Leinninger, 2009; Opland et al., 2010). Central administration of leptin into the VTA decreases food intake, reduction of leptin receptors within VTA neurons increases food intake and also increases acute intake of palatable high-fat food (Davis et al., 2010). Together, these results suggest that leptin signaling within the VTA is capable of modulating normal and hedonic feeding behavior (Fiiglewicz and Sipols, 2010). Leptin also acts in extrahypothalamic tissues as a neuroprotective agent (Harvey, 2007a; Signore et al., 2008; Folch et al., 2012). Moreover, leptin promotes rapid remodeling of hippocampal dendrites, what may contribute to cognitive functions, as well (Harvey, 2007b; O'Malley et al., 2007).

Concerning energy homeostasis, direct central (intracerebroventricular, ICV) administration of leptin in animal experiments induced a combined action (Pétervári et al., 2014). In ad libitum fed young adult rats the centrally applied peptide caused anorexia with simultaneous sympathetic activation, enhanced brown fat activity and hypermetabolism, collectively regarded as a catabolic effect. Indeed, body weight and fat content decreased upon central leptin infusion in ad libitum fed animals. The lack of leptin effects, on the other hand is known to cause obesity.

During the course of aging (or in obesity), in addition to the regulatory role of the BBB in the entry of leptin into the hypothalamus, reduced receptor expression may also contribute to the development of central leptin resistance. Indeed, in old rats, immunohistochemical and Western blot analyses showed a lower amount of the LEPR-B in the hypothalamus and RT-PCR confirmed a decreased expression of leptin receptor mRNA (Fernández-Galaz et al., 2001). Additionally, alterations in signal transduction pathways (that are discussed below) may contribute to the development of age-associated central leptin resistance.

Accordingly, in addition to obesity and dysregulation of energy balance, central leptin resistance also affects various cerebral functions, among others, motivated (hedonic) behavior or age-related cognitive decline (Harvey, 2007b; Davis et al., 2010). Indeed, obesity has already been proven to be an important factor in the pathogenesis of Alzheimer's disease, independently of insulin resistance or other vascular risk factors (Letra et al., 2014).

2.1. Signal transduction pathways of leptin

In neurons, the effects of leptin are mediated by LEPR-B, a splicing variant member of the class I cytokine receptor family. This variant has a long cytoplasmic region allowing the activation of the JAK2-STAT3/STAT5 (Janus kinase-2/signal transduction and activator of transcription-3 or 5) signal transduction pathways that are crucial for leptin actions in energy homeostasis (Tartaglia, 1997; Friedman and Halaas, 1998). LEPR-B is predominantly located in the hypothalamic ARC and other hypothalamic regions known to be involved in the regulation of energy balance (Mercer et al., 1996; Schwartz et al., 1996b; Elmquist et al., 1998).

Following binding to its LEPR-B leptin activates JAK2. In turn, JAK2 phosphorylates LEPR-B on various tyrosine residues (Tyr985, Tyr1077 and Tyr1138). They (phospho-Tyr985, -Tyr1077 and -Tyr1138) bind to downstream molecules and activate the JAK2/STAT3, JAK2/STAT5, and additionally the phosphatidylinositol 3-kinase/insulin receptor substrate/AKT kinase (PI3K/IRS/AKT), and SH2 domain of protein tyrosine phosphatase 2/extracellular signal-regulated kinase (SHP2/ERK) pathways (Zhou and Rui, 2013).