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Critically Discuss the Revival of Leptin for Obesity Therapy

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Abstract

Obesity has created a very serious public health problem, and World Health Organisation has actually warned that there is an urgent need for multinational cooperation to stem the rise of obesity. More than 20 years ago the discovery of Leptin, which is an adipocyte-secreted hormone and primarily acts on the hypothalamic neurons to activate the regulation of energy homeostasis, created much interest in its potential use for the treatment of obesity, but the hope was soon lost after leptin failed to counteract common diet-induced obesity. In recent years some preclinical studies have surprisingly demonstrated that resistance to leptin can be reversed and the effects of leptin therapy can be amplified by several leptin sensitisers. This paper will critically discuss the plausible revival of leptin for obesity therapy with reference to research findings on various influencing factors contributing to the level of expression and secretion of leptin.

Keywords

Obesity, Energy Homeostasis, Leptin Difficency, Leptin Resistance, Leptin Sensitisers, Leptin Receptors

1. Introduction

The Body Mass Index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. Adults with BMI ≥ 25 are defined as being overweight, and those with BMI ≥ 30 are obese (WHO, 2017). In accordance with a recent report of World Health Organization (WHO, 2016) obesity has become a serious global epidemic. In 2016 over 650 million adults aged 18 years and older were obese, meaning that the prevalence of obe-

sity has almost tripled around the world for the past four decades. Obesity is the fifth leading risk for global deaths because numerous studies have shown that obesity is closely associated with various chronic diseases, namely type-2 diabetes mellitus (Konner & Bruning, 2012), cardiovascular diseases (Patel et al., 2008), immunity and inflammation (DeLany, 2008; Duntas & Biondi, 2013), psychological deficits (Milaneschi et al., 2012; Yamada-Goto, et al., 2012), and some malignancy conditions (Pasquali & Gambineri, 2006) such as colorectal cancer (Na & Myung, 2012) and breast cancer (Wauman & Tavernier, 2011). Thus, obesity has created a very serious public health problem, and medical costs associated with it are soaring high. In view of such an overwhelming health crisis, WHO (2016) has actually warned that there is an urgent need for multinational cooperation to stem the rise of obesity.

Leptin, which is an adipocyte-secreted hormone, was discovered more than 20 years and primarily acts on the hypothalamic neurons to activate the regulation of a balance between food intake and energy expenditure (Zhang et al., 1994; Halaas et al., 1995; Ingalls et al., 1996; Moon & Friedman, 1997; Friedman & Halaas, 1998). Obviously the discovery of leptin created much interest in its potential use for the treatment of obesity, but the hope was soon lost after leptin failed to counteract common diet-induced obesity (Halaas et al., 1997; Widdowson et al., 1997; Heymsfield et al., 1999; Levin et al., 2002). Nevertheless, overcoming resistance to the leptin therapy continues to challenge the researchers. In recent years some preclinical studies have surprisingly demonstrated that resistance to leptin can be reversed and the effects of leptin therapy can be amplified by several *leptin sensitisers* (Moon et al., 2011; Müller et al., 2012; Matthias, 2014; Crujeiras et al., 2015; Park & Ahima, 2015). Accordingly, it is the aim of this paper to critically discuss the plausible revival of leptin for obesity therapy with reference to research findings on various influencing factors contributing to the level of expression and secretion of leptin.

2. Energy Homeostasis and Leptin Deficiency

Obesity is an eating disorder accompanied by an imbalance between energy consumed and energy expended. According to WHO (2017) the energy imbalance is attributed to both an increased consumption of energy-dense foods and an increase in physical inactivity. Both dieting and physical training have naturally become the most common behavioural weight loss programmes. However, none of these programmes has thus far proven to be effective in achieving the long-term weight loss (Kramer et al., 1989; Wooley & Garner, 1994; Curioni & Lourenco, 2005), implying that the exact causes of obesity are still unclear. A growing number of researchers have thus turned their attention to the study on the physiological mechanisms which normally regulate food intake and body weight, in the hope of identifying the real causes of obesity and discovering effective therapies (Maffei et al., 1995; Myers, et al., 2010; Wauman & Tavernier, 2011; Myers, et al., 2012; Panariello et al., 2012; Wong et al., 2013; Ottaway et al.,

2015).

It is interesting that in most adults body weight is almost constant in spite of a large variation in daily food intake and energy expenditure (St-Pierre & Tremblay, 2012). Indeed, body weight is generally maintained within a narrow range by regulating a balance between energy intake, in the form of food and drinks, and energy expenditure, in the form of basal metabolism, physical activity and adaptive thermogenesis, via the adipose-tissue-brain crosstalk (Schwartz et al., 2000; Rosen & Spiegelman, 2006; Tao et al., 2011). When energy imbalance occurs, excessive calories accumulate as triglycerides in adipose tissue, leading to overweight and obesity. Hence, a better understanding of the energy homeostasis in a human body holds the key to finding the exact causes of obesity (Paspala et al., 2012; Szczesna et al., 2013; Chopra et al., 2014; Pan et al., 2014; Crujeiras et al., 2015; Park & Ahima, 2015; Sáinz et al., 2015).

Energy homeostasis is a physiological process that controls energy balance via a complex interaction between the central nervous system (CNS) and peripheral tissues by constantly monitoring energy availability, storage and consumption (Morris & Rui, 2009). The crucial player in the CNS controlling food intake is the hypothalamus located in the base of the brain (Elmquist et al., 1999; Cone, 2005). More specifically, ventromedial hypothalamus is associated with satiety and inhibiting food intake, whereas lateral hypothalamus is associated with hunger and increasing food intake. On the other hand, the adipocyte derived hormone leptin, that has proven to be a key marker of the energy storage in the body, provides the adiposity signals to the hypothalamus which subsequently integrates these signals and regulates the energy homeostasis by maintaining a balance between food intake and energy expenditure (Zhang et al., 1994; Halaas et al., 1995; Ingalls et al., 1996; Moon & Friedman, 1997; Friedman and Halaas, 1998). Ample evidence has shown that genetic leptin deficiency or lack of functional leptin receptors in mice causes morbid obesity and type 2 diabetes (Zhang et al., 1994; Tartaglia et al., 1995) whilst congenital leptin deficiency results in severe hyperphagia and early-onset obsesity in humans (Montague et al., 1997; Strobel et al., 1998; Farooqi et al., 1999). In addition, a leptin replacement therapy significantly helps ameliorate obesity-associated metabolic disorders in those leptin-deficient patients (Zhang et al., 1994; Farooqi et al., 1999; Farooqi et al., 2002; Gibson et al., 2004; Licinio et al., 2004), thus confirming the *leptin deficiency hypothesis* and that normal leptin production and action are critical for maintaining energy balance.

3. Leptin Therapy and Leptin Resistance

In spite of the enormous hopes raised by the leptin therapy for human obesity, a large number of studies have demonstrated that most obese humans exhibit abnormally high levels of circulating leptin rather than a deficiency in leptin (Maffei et al., 1995; Considine et al., 1996; Scarpace et al., 2009) and that the administration of exogenous leptin fails to counteract common obesity (Halaas et al.,

1997; Widdowson et al., 1997; Heymsfield et al., 1999; Levin et al., 2002). These obese patients are hypothesized to develop *leptin resistance* that is commonly defined by the reduced capability of leptin to resist the development of obesity (Enriori et al., 2006; Morrison, 2008; Myers et al., 2008; Bjorbaek, 2009; Morris & Rui, 2009; Wong et al., 2013). Since the lack of response to leptin hinders central and peripheral actions of leptin, including appetite, nutrient intestinal absorption, intermediate metabolism and insulin sensitivity, and subsequently leads to an energy imbalance and weight gains, much attention has been attracted to elucidating the underlying molecular mechanisms of leptin resistance and the possibility of correcting the resistance in the scientific community. Currently, although the actual underlying mechanisms remain subject to debate, two possible mechanisms have gained most attention to date, namely impairment in leptin transportation across the blood-brain barrier (BBB) and impairment in leptin signal transduction in the hypothalamic neurons (El-Haschimi et al., 2000; Morris et al., 2010; Coppari & Bjorbaek, 2012). Besides, other factors, including inflammation or oxidative stress proceeses (Leon-Cabrera et al., 2013), a desensitization of cellular downstream signalling at central and peripheral level (Munzberg et al., 2005), and the type of diet (Shapiro et al., 2011), may also contribute to leptin resistance.

Extensive experimental results demonstrate that obese subjects exhibit high levels of peripheral leptin and relatively lower levels of leptin in cerebrospinal fluid (CSF), suggesting impairment in leptin transportation into the CNS across the BBB (Caro et al., 1996; Schwartz et al., 1996; El-Haschimi et al., 2000; Hileman et al., 2002; Banks & Farrell, 2003; Levin et al., 2004). As leptin is a large molecule, a protein of 16kDa, its transfer across the BBB is aided by a transport system. Thus, high circulating leptin levels in the obese condition may cause saturation of leptin transporters in the saturable transport system and compromise further leptin uptake by the brain (Caro et al., 1996). Since leptin mediates the signals for energy homeostasis (that is, inhibition of appetite and increased energy expenditure) only under the conditions that circulating leptin is transported across the BBB and ultimately binds to its receptors, the capability of leptin in regulation of appetite and energy expenditure is drastically reduced (El-Haschimi et al., 2000). As a result, the impaired leptin transport rates across the BBB have both chronic and acute influences on body weight. Moreover, the balance of leptin transport process is regulated by two leptin receptors (LEPRs), namely ObRa and ObRe. The ObRa mediates leptin transport across the BBB (Hileman et al., 2000; Tu et al., 2008) whereas the ObRe inhibits leptin transport by counteracting the function of ObRa (Bjorbaek et al., 2000). Under normal conditions the actions and numbers of both LEPRs are in balance. Accordingly, further studies to clarify the correlation between these two LEPRs under both normal and obese states are highly desirable for they will shed light on how to maintain the balance.

Another possible mechanism of leptin resistance is impairment in leptin sig-

nal transduction in the hypothalamic neurons. It has been observed that administration of exogenous leptin produces strong immunoreactivity of phosphorylated signal transducer and activator of transcription 3 (STAT3) in the hypothalamic neurons of the arcuate nucleus (ARC) (Hubschle et al., 2001), and that in diet-induced obese mice leptin-induced STAT3 phosphorylation is greatly reduced in the hypothalamus (El-Haschimi et al., 2000). In response to leptin signalling, activated STAT3 in turn induces expression of the suppressor of cytokine signalling 3 (SOCS3) protein (Banks et al., 2000), which has been found to play an essential role in suppressing leptin signal transduction (Reed et al., 2010). Hence, enhanced hypothalamic SOCS3 expression is believed to be responsible for obesity-induced impairment of hypothalamic leptin signalling.

4. Multi-Therapy of Leptin

Beyond question leptin as a stand-alone drug is not capable of providing an effective treatment of obesity. However, in recent years researchers have demonstrated that a multi-therapy of leptin in combination with other leptin sensitisers may be able to improve peripheral leptin sensitivity and may hold therapeutic promise (Moon et al., 2011; Müller et al., 2012; Matthias, 2014; Crujeiras et al., 2015; Park & Ahima, 2015). These leptin sensitisers target distinct neuroendocrine systems related to leptin signalling pathology. For instance, amylin and leptin, tri-infusion of cholecystokinin, leptin and amylin, and glucagon-like peptide 1 and leptin therapies are able to suppress food intake and enhance body weight loss than leptin monotherapy (Bhavsar et al., 1998; Roth et al, 2008; Trevaskis et al., 2008; Trevaskis et al., 2010; Yan et al, 2015). Alternatively, leptin-related analogues which are capable of binding and activating the active leptin receptor OBR can be used to help solve some problems associated with natural leptin such as the issue of leptin being inactive, low stability and short half-life (Roujeau et al., 2014).

In addition, gastrointestinal derived peptides and a series of already approved pharmaco therapies have been found to amplify the weight-lowering actions of exogenous leptin (Wang et al., 2000; Kim et al., 2006; Roth et al., 2008; Unniappan & Kieffer, 2008; Müller et al., 2012). Likewise, several research groups have investigated blocking those negative regulators of leptin signalling such as SOCS3 and the phosphor-tyrosine protein phosphatase PTP 1B to improve the leptin response in obese persons (Kaszubska et al., 2002; Reed et al., 2010; Roujeau et al., 2014). Furthermore, co-administration of leptin with either exendin-4 or FGF21 has been shown to restore leptin responsiveness in diet-induced obese mice (Kim et al., 2006; Müller et al.; 2012).

5. Conclusion

In spite of the impossibility of using leptin as a stand-alone magic bullet for obesity therapy, combination therapy for obesity seems to provide a glimpse of hope in pharmacotherapy. Since physiological mechanisms resisting weight loss are

anticipated during leptin monotherapy, it is apparent that targeting more than one mechanism will naturally enhance the chance of success in the treatment of obesity. Hence, if we continue to work hard to advance our knowledge of the underlying mechanisms of leptin resistance steadily, the pursuit of identifying optimal combination therapies will become much more promising.

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