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The Sympathetic Neuro-Adipose Connection and the Control of Body Weight

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Abstract

In recent decades, obesity has become a global public health crisis irrespective of age or gender (Ng et al., 2014). But according to historic records, concerns over appropriate maintenance of body size have been long established. For more than to 2 millennia, the main therapeutic approach to curb excess weight has been to recommend dietary restrictions and regular exercise (Haslam, 2016). Nevertheless, more contemporary studies indicate that the employment of such approaches in the treatment of severely obese patients causes metabolic adaptions which impair their long-term success in weight management (Fothergill et al., 2016). These evidences highlight thus, the urgency in the search for a more comprehensive knowledge of the mechanisms that underlie the control of body weight, which would be essential for the development of effective strategies for the treatment of obesity and its comorbidities. Importantly, the discovery of the hormone leptin (Zhang et al., 1994) and the use of novel techniques in targeted transgenesis (Zeng et al., 2015) have enabled progress in defining some of the key players and the molecular mechanisms that are involved in the processes that control body size homeostasis and energy balance, and how obesity may disrupt leptin's feedback loop and lead to the pathology of metabolic syndrome. On the light of such findings, here we review how the sympathetic nervous system modulates adipose tissue metabolism downstream of leptin's action on the CNS, with particular focus on how this system may be disrupted in the context of excess adiposity, plus highlight the potential clinical implications arising from a better understanding of the physiologic control of the sympathetic neuro-adipose connection.

Keywords

leptin; obesity; sympathetic neurons; neuro-adipose connection

Introduction: Leptin as the master regulator of body weight

Historically, excess weight, obesity and the control of body size have always been object of general attention and speculation (Haslam, 2016). Ancient Greeks appreciated that obesity originated from an imbalance between energy intake and energy expenditure, and even noted it would increase the risk for other illnesses. Similar to today's philosophy, a balanced diet

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coupled with increased exercise was recommended as the main therapeutic strategy for healthy weight management (Hippocrates and Smith, 1994). However, exposure to modern life-styles, associated with sedentariness and easy access to high energy dense foods and drinks, has caused worldwide prevalence of obesity to rapidly increase, nearly doubling between 1980 and 2016 (WHO, 2016). This reality highlights how poorly effective the strategy of diet and exercise are in restoring energetic balance to overweight individuals. It has now become apparent how much still needs to be explored when therapeutically managing the dynamics of body weight regulation.

There is however, a consensus in the scientific community that amongst the genetic and environmental factors known to control the maintenance of body weight, the hormone leptin stands out as the master regulator. This is due to the circulating levels of leptin being proportional to adipose tissue size and functioning as the afferent signal in a negative feedback loop that maintains adiposity in a very narrow range of variation, by its effect in food intake inhibition and energy expenditure increase (Friedman and Halaas, 1998). Furthermore, it is well established that the lipostatic effect of leptin is mostly owing to its engagement of downstream pathways of the leptin receptors concentrated in the hypothalamus. (Mizuno and Mobbs, 1999; Seeley et al., 1997). Nevertheless, most obese subjects are not only hyperleptinemic, they are also leptin resistant, i.e. they typically have excessive amounts of the hormone in circulation, but this fails to reduce body weight and maintain proper energy balance. This phenomenon has been under intense focus in obesity studies, shedding light on the many mechanisms involved in the development of leptin resistance (Martin et al., 2008; Myers et al., 2010). However, our understanding of the involvement of hyperleptinemia in the development of impaired satiety is far more understood than that which is responsible for the loss of the lipolytic action of leptin (Sáinz et al., 2015). Hence, this review will focus on leptin's modulation of sympathetic drive in adipose tissue, inducing downstream lipolysis, thermogenesis and browning cellular programs, and the role of the sympathetic nervous system (SNS) in the pathophysiology of obesity.

Leptin in the regulation of the SNS output

Leptin acts on the hypothalamus not only to suppress appetite, but also to increase energy expenditure. The of hypothalamic leptin receptor's starts a cascade that elevates SNS output leading to the postsynaptic activation of adrenergic receptors in innervated organs throughout the periphery (Seoane-Collazo et al., 2015). In fact, this elevation of SNS tone by leptin is proposed to be essential for its effective lipostatic action, mainly through the induction of lipolysis in white adipose tissue (WAT), as well as thermogenesis in brown adipose tissue (BAT) and browning of WAT (Thorp and Schlaich, 2015). Consistent with this idea, is the hypothesis that we could manipulate SNS output in the neuro-adipose connection, driving the consequent induction of lipolysis (WAT) and/or thermogenesis (BAT and WAT), as a very specific therapeutic target in the context of obesity management. To reach this end a greater understanding of leptin's control of SNS output to adipose tissue and how the loss of energy expenditure due to leptin resistance develops, consequently driving the well-known progression of obesity into metabolic syndrome.

In fact, in a recent study, sympathetic neuro-adipose junctions were directly visualized by multi-photon microscopy, where the neuronal projections completely envelop the adipocyte and synapse onto it. Here, it is also shown that local gain-of-function of sympathetic neuronal activity in the inguinal fat pad drives local lipolysis and local reduction of fat mass. Conversely, local loss-of-function of sympathetic neurons in the fat pad abrogates leptin´s lipolytic action in a local manner (Zeng et al., 2015). Furthermore, leptin's recruitment of SNS has also been described to strongly participate in the glycaemic control via adrenergic signalling engagement in BAT, which results in activation of thermogenesis and the associated increase in glucose uptake (Fujikawa et al., 2013). The relevance of understanding this control of both adipose tissue metabolism and glucose homeostasis should then be highlighted as a crucial target for the treatment of obesity and prevention of the development of metabolic syndrome.

The Leptin-SNS loop in Obesity

Obesity is widely accepted to be driven by leptin resistance, with consequently low SNS output and lipolytic drive in adipose tissue. Human studies of leptin treatment have described the effect of leptin therapy on body weight control, through regulation of both food intake and energy expenditure, is differently exerted in lean and obese subjects, suggesting different sensitivity to the hormone (Dodt et al., 2003). Nevertheless, leptin resistance observed in the context of obesity is the major risk factor for the development of metabolic syndrome, for which the diagnosis highlights the connection between the elevation of metabolic markers (abdominal obesity, hyperlipidemia and hyperglycemia) and of the risk for developing cardiovascular diseases, due to increase SNS tone (Schlaich et al., 2015).

Although it seems counter-intuitive, in obese subjects, leptin resistance could also be associated to chronic increase of sympathetic tone. This explains the development of obesity associated hypertension and other cardiovascular morbidities which lead to metabolic syndrome. In humans, these associations where based on observations that in obese subjects there is increased urinary norepinephrine (NE), efferent muscle sympathetic nerve activity (MSNA) and NE spillover (global and regional) to the plasma (Bartness et al., 2014). Such increase of SNS tone seems to be differentially distributed across organs, such as heart, blood vessels, muscles or various fat depots. Indeed, the heart, kidney and muscle seem to be the major targets of increased sympathetic tone in obesity, linked to the development of hypertension, while limited lipolytic responsiveness to SNS-mediated stimuli in WAT and BAT. This might explain the impaired ability to use fat stores and progression of the disease (Davy and Orr, 2009). Hence, there is a need for a more comprehensive understanding of how leptin drives SNS activity than what we currently have, enabling a more effective design of obesity treatment.

Obesity and the SNS output to the adipose tissue

Among the regulators of WAT sympathetic drive, leptin stands out due to the 20 years of accumulated knowledge since its discovery, and this hormone has even been approved as obesity therapy in leptin-deficient individuals (Friedman and Mantzoros, 2015).

Furthermore, central administration of leptin doses increases the sympathetic activity on WAT and the lipolytic response induced by intraperitoneal injections of leptin is prevented by the administration of β-blocker propranolol, suggesting that leptin's lipolytic effect on WAT is mediated by NE binding to β-adrenergic receptors in adipocytes (Shen et al., 2007).

BAT is also regulated by NE binding to β-adrenergic receptors, which, then promotes the dissipation of chemical energy via thermogenesis. This is accomplished by the expression of Uncoupling Protein 1 (*UCP1*), an anion-carrier protein that enables proton leak disrupting the membrane potential and uncoupling oxidative phosphorylation from ATP production. The result is high energetic spending in BAT leading to dissipation of the proton gradient energy in the form of heat (Krauss et al., 2005). In addition, it has also been shown that specific engagement of leptin's receptor pathway and consequent SNS output in BAT promotes the expression of *GLUT4* mRNA in this tissue, chronically improving glucose tolerance in mice (Morgan et al., 2015).

Besides the classical descriptions of BAT as an anatomically isolated organ, brown-like adipocytes have been identified on WAT depots of mice acclimated to cold. This is shown by expression of *UCP-1* and the characteristic higher mitochondrial crista density and multilocular appearance. As the content of UCP-1 in the fat depots is induced by specific stimuli, such as cold exposure, it suggests that WAT metabolic features can adapt as the body's energetic demands change (Bartness and Ryu, 2015). This process, termed "browning", has raised hope in finding new therapeutic strategies in obesity, by increasing the thermogenic potential of WAT and thus total energy expenditure, forcing lipid mobilization and adiposity reduction. The common stimuli for browning seems to be adrenergic induction, either via natural sympathetic drive caused by cold or fasting or via β3-agonists administration. The role of these receptors for browning induction has been confirmed with studies in β3-KO mice, where the animals acclimated to cold environment for 10 days showed decreased expression of *UCP-1* and density of multilocular cells when compared with their wild-type counterparts (Jimenez et al., 2003). Furthermore, the number of sympathetic nerve fibers in contact with multilocular adipocytes in WAT depots increased 3-fold in cold-acclimated mice and a correlation could be discerned between the density of TH-positive fibers and the number of brown adipocytes(Vitali et al., 2012).

SNS action on adipose tissue is therefore very relevant for the understanding and thus treatment of obesity and its comorbidities. Yet, it is important to note, that the existence of local catecholamine resistance, associated with decreased expression of specific β-adrenergic receptors in the adipose tissue of obese individuals has long been established (Collins et al., 1999). However, it is still unclear how the resistance mechanisms (both leptin and catecholamine) are physiologically triggered; and it is completely unknown whether the peripheral mechanisms are more or less relevant than hypothalamic leptin resistance for the loss of the lipostatic effect of leptin-SNS-WAT/BAT system result in the disruption of proper maintenance of bodyweight and the development of obesity and metabolic syndrome.

Obesity and the SNS output to other targets

Besides the already known environmental factors (diet and exercise) and genetic predisposition, the SNS is also recognized as having a significant impact in the development

of obesity related comorbidities., although seemingly opposing theories have been formed to explain the sympathetic involvement. On one side, the MONALISA hypothesis (Most Obesity kNown Are Low In Sympathetic Activity) postulates that impaired sympathetic activity lies behind the development of obesity, by shifting the energy balance towards storage, in detriment of thermogenesis (Bray, 1991). This theory, which precedes leptin's discovery, was based on reports of hypothalamic lesions in mice which decrease SNS tone leading to obesity. In fact, lower sympathetic activity correlates well with lower basal metabolic rate, representing a decrease in total energy expenditure (Spraul et al., 1993).

On the other side, obesity has also been associated with a chronic increase of sympathetic tone to the cardiovascular system, which could explain the development of obesity related hypertension and other cardiac abnormalities (Davy and Orr, 2009). Moreover, the distribution of fat into different depots appears as a major factor in determining SNS hyperactivity, with abdominal visceral adiposity playing the most confounding role. Indeed, the correlation between abdominal visceral fat volume and MSNA is apparent not only in obese but also normal weight subjects, while subcutaneous adipose mass was not correlated to MSNA (Alvarez, 2004). According to Landsberg original hypothesis, the increase of SNS activity in obese individuals serves the purpose of counteracting the positive energy balance, by increasing resting energy expenditure and preventing weight gain (Landsberg and Young, 1978). It is also relevant to point that, in the context of obesity, besides leptin, other master regulators of SNS output to the cardiovascular system have also been suggested to function as mechanistic triggers of sympathetic activity, namely the pancreatic hormone insulin and the renin-angiotensin-aldosterone axis (Davy and Orr, 2009).

Future perspectives

In conclusion, for the development of efficient therapies, there is still a need for a more complex understanding of how hyperleptinemia, associated with leptin resistance, drives obesity and promotes metabolic syndrome and related comorbidities. Perhaps, the key for successful weight loss and long-term weight management for obese patients, is not the curbing of the energy intake axis of the energetic balance, but in the restoration of the resting energy expenditure that is loss upon leptin resistance. Hence, it is important to clarify the mechanisms that underlie the specific loss of SNS activity in the adipose tissue (both WAT and BAT) in opposition to the elevation observed in other tissues (heart and kidneys). In fact, a clinical strategy that has been employed in the treatment of obesity is the activation of the SNS to stimulate lipolysis and counteract the reduced thermogenesis that occurs during caloric restriction using sympathomimetic drugs. Unfortunately, these drugs are only approved for short-term use as they have side effects of increased cardiac contractility and high blood pressure (Schlueter et al., 2014). This therapeutic approach is thus paradigmatic of the problem of finding pharmacological targets that are specific of the adipose tissue and circumventing the induction of sympatho-excitatory adverse effects on the cardio vasculature.

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