Editorial Comment

Does Genetic Variation in the Leptin Receptor Influence the Sympathetic Tone in Obesity?

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The prevalence of obesity is increasing at an alarming rate throughout the world. Obesity is a serious health problem because weight gain is associated with a high risk of developing various diseases such as type 2 diabetes, some cancers and cardiovascular disorders including coronary heart disease, hypertension and endothelial dysfunction (*1*). The discovery of leptin in 1994 has allowed a tremendous advance in the endocrinology of energy homeostasis and the neurobiology of obesity. Leptin is an adipocyte-derived hormone whose circulating concentration is proportional to the level of body fat (*2*). This hormone is considered to be a critical signal that feeds back to inform the central nervous system about the status of peripheral energy reserves. The severe obesity and hyperphagia caused by the absence of leptin or its receptor in rodents and humans make it clear that this hormone is fundamental for the control of body weight and energy homeostasis (*2–4*). However, mutations in the genes that encode leptin or the leptin receptor are rare and most obese humans and rodents do not have low circulating leptin, but are hyperleptinemic, reflecting a state of leptin resistance just like hyperinsulinemia in type 2 diabetes is interpreted to reflect a state of insulin resistance.

The understanding of the biological actions of leptin has increased exponentially during the recent years. Leptin is now recognized to have a broader range of actions with physiological implications that far surpass its influence on energy homeostasis. For instance, leptin is known to influence every aspect of reproduction including puberty onset, fertility and pregnancy (*5*, *6*). Leptin also plays an important role in the neuroendocrine response to calorie restriction and starvation by modulating the hypothalamic pituitary function and the thyroid, adrenal and growth hormone axes (*7–9*). Leptin action in the central nervous system causes widespread activation of the sympathetic nervous system (*10–12*). The finding that leptin deficiency in humans is associated with decreased sympathetic tone and hypotension provides strong evidence for the importance of leptin for the control of the sympathetic nervous system (*4*).

Emerging evidence supports a pathophysiological role for leptin in the hypertension associated with obesity because leptin resistance in the central nervous system appears selective. Indeed, the ability of leptin to activate the renal sympathetic nerve activity and increase arterial pressure is preserved in obesity despite the resistance to the metabolic actions of leptin (*13*). In the context of high circulating levels of leptin associated with obesity such selective leptin resistance could predispose to obesity-related hypertension and other cardiovascular diseases (*14*).

In the current issue of *Hypertension Research*, Masuo *et al.* (*15*) examined whether genetic variation in the leptin receptor may contribute or determine the level of fat mass and sympathetic nerve activity in a Caucasian male population. The leptin receptor is a member of the cytokine family of receptors that have a single transmembrane domain. Alternative splicing of a single transcript encoded by the leptin receptor gene, mapped to 1p31, produces six different isoforms of the leptin

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receptor. The ObRb form with a long 302-residue intracellular domain appears to mediate most of the biological effects of leptin (*16*, *17*). The leptin receptor gene contains a number of single nucleotide polymorphisms. Masuo *et al*. analyzed the relationship between three common polymorphisms in the leptin receptor gene (Lys109Arg, Gln223Arg and Lys656Asn), obesity, sympathetic nerve activity and blood pressure in 129 healthy male individuals (*15*).

As expected, in comparison to the lean controls (body mass index [BMI] <25 kg/m^2) the overweight/obese subjects (BMI ≥ 25 kg/m^2) had higher sympathetic tone (determined by whole-body norepinephrine spillover) and mean blood pressure. Interestingly, this analysis also revealed a significantly higher prevalence of the Arg223 allele in the homozygous form and Asp656 allele in the overweight/obese subjects (*15*). In contrast, no difference was found in the genotype frequencies for the Lys109Arg polymorphism between subjects that are overweight/obese and lean. Further analysis showed the Arg223 and Asp656 alleles to be associated with a higher fat mass as reflected by the increase in BMI, markers of central obesity and plasma leptin. Surprisingly, despite the increased signs of obesity, subjects carrying the Arg223 and Asp656 alleles have a lower sympathetic nerve activity and a normal blood pressure (*15*). The sympathetic nervous system is an important regulatory mechanism of the metabolic function. Therefore, the decreased sympathetic tone in the subjects carrying the Arg223 and Asp656 alleles is consistent with the increased fat mass observed in these subjects.

With regard to obesity, the results of this study correlate with the findings of previous studies demonstrating that sequence variations in the leptin receptor gene could affect adiposity, body weight and metabolism (*18–20*). However, there are some discrepancies in the findings linking leptin receptor polymorphisms and metabolic parameters, perhaps due to differences in the gender, ethnic background and age of the populations that were considered in each study. With respect to sympathetic tone and blood pressure, the results described by Masuo *et al*. (*15*) complement and extend the findings of previous reports that analyzed the role of the leptin receptor gene polymorphism in the sympathetic and cardiovascular perturbations associated with obesity. For instance, Guizar-Mendoza *et al*. (*21*) showed Mexican adolescents with the Gln223 allele of the leptin receptor to have a higher cardiac sympathetic nerve activity measured by electrocardiography at rest. On the other hand, Rosmond *et al*. (*22*) found that Caucasian carriers of the leptin receptor with the Arg109 or Arg223 alleles in the homozygous form had a lower blood pressure independent of any other variables. In addition, these authors showed the sequence variations in the leptin receptor gene to play a role in the association between obesity, plasma leptin and blood pressure and they may also be involved in the predisposition to obesity- and hyperleptinemia-induced hypertension. Altogether, these findings seem to suggest that genetic variation in the leptin receptor is a key determinant in the development of obesity-associated sympathetic activation and hypertension and they could also explain why some obese subjects are not hypertensive.

The mechanisms by which polymorphisms in the leptin receptor gene could affect the various physiological functions remain to be determined. It is possible that a variation in the amino acids influence the binding capacity of the leptin receptor and/or the ability of the receptor to activate the downstream intracellular pathways. For instance, the Gln223Arg polymorphism is located within the region encoding the extracellular domain of the leptin receptor and this polymorphism has been shown to change the functional characteristics of the receptor. Indeed, the leptin receptor variant homozygous for the Arg223 allele seems to have a reduced binding capacity (*23*). Understanding how leptin receptor gene polymorphisms affect physiological processes will expand our present knowledge concerning the genetic factors that influence fat mass and the predisposition to obesity. This could also lead to new therapeutic strategies that target specific variants of the leptin receptor for the treatment of obesity.

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